EXHIBIT 49

CTEH®

EXPERT REPORT OF PAUL A. NONY, PHD, CIH, CSP

In the Matter of Johnson & Johnson Talcum Powder Products Marketing, Sales Practice, and Products Liability Litigation

May 28, 2024

Table of Contents

List of Tables

List of Appendices

1.0 INTRODUCTION AND QUALIFICATIONS

I am a Principal Toxicologist and Senior Vice President at CTEH, LLC (CTEH®). CTEH® has several specialties, including toxicology, human health risk assessment, industrial hygiene, indoor air quality, and emergency response.

I hold a Bachelor of Arts degree in Biology from Hendrix College in Conway, Arkansas (1996) and a Ph.D. degree in Interdisciplinary Toxicology from the University of Arkansas for Medical Sciences (2001). Since receiving my Ph.D. in Interdisciplinary Toxicology, I have been actively involved in the areas of toxicology and industrial hygiene. From 2001-2003 as a postdoctoral fellow, I conducted human cancer research at the National Institute of Environmental Health Sciences in Research Triangle Park, NC. Since 2003, I have been active at CTEH® as a consultant in the areas of human and environmental toxicology and industrial hygiene and have been involved in numerous projects involving the assessment of chemical exposures and their effects on humans. As a toxicologist, I routinely assist in the determination of disease causation by evaluating chemical exposures and the scientific evidence relating exposures to human diseases according to the methodology of toxicological causation analysis. In addition, I am certified in the comprehensive practice of industrial hygiene by the American Board of Industrial Hygiene (CIH #11135CP) and am a Certified Safety Professional (CSP #33934) as determined by the Board of Certified Safety Professionals.

I am a member of the Society of Toxicology, the South Central Chapter of the Society of Toxicology, the Occupational and Public Health Specialty Section of the Society of Toxicology, the American Industrial Hygiene Association, and the American Conference of Governmental Industrial Hygienists. I have written numerous peer-reviewed publications in toxicology and related fields. A list of my publications is included within my attached curriculum vitae (**Appendix A**).

Toxicology, a blend of biology, chemistry, and medicine, is the science of the adverse effects of substances (e.g., chemicals, physical agents, drugs) on biological systems including the effects, the recognition, and the mechanisms of a chemical-related disease. Whether a substance is toxic depends upon two inseparable criteria: 1) the intrinsic nature of the substance, and 2) the dose, or how much of a substance the individual actually takes into their body. In toxicology, we study the dose-response of chemicals on biological systems, with emphasis on understanding the mechanisms of harmful effects. Toxicologists also provide expert opinions with respect to causation in toxic tort litigation. As stated by the Federal Reference Manual on Scientific Evidence (NRC, 2011, p. 398), "*In tort litigation, toxicologists offer evidence that either supports or refutes plaintiffs' claims that their diseases or injuries were caused by chemical exposures.*"

The opinions stated in this report are based on my education, training, and experience in the fields of toxicology and industrial hygiene and my review of the referenced information. All of my opinions in this report are stated to a reasonable degree of toxicological and scientific certainty.

2.0 UNDERSTANDING OF ALLEGATIONS

I have been asked to offer an opinion regarding the alleged association between exposure to cosmetic talcum powder and ovarian cancer from the perspective of a toxicologist based on the relevant scientific literature and my knowledge, training, and experience as a toxicologist and industrial hygienist. This includes an assessment of the alleged presence and carcinogenicity of certain constituents in talcum powder, including asbestos, fibrous talc, select heavy metals, and fragrance chemicals. I have also been asked to review the opinions and methodology of certain plaintiffs' experts and to opine on the validity and reliability of their causal assessments in connection with talc litigation.

The opinions set forth in this report are stated to a degree of reasonable scientific certainty based on my education, training, and experience in the fields of toxicology and industrial hygiene, and on my review of the information referenced in my report. CTEH® is being compensated for my time at a rate of $535 per hour.

3.0 MATERIALS REVIEWED AND RELIED UPON

In formulating my opinions, I have relied upon and/or reviewed information from the pertinent scientific literature and other information listed in **Appendix B** to this report. I reserve the right to supplement this report, including the opinions stated herein and the materials listed in Appendix B, as necessary if additional information is made available to me.

4.0 SUMMARY OF OPINIONS

Opinion 1 – Scientific literature examining the association between cosmetic talc and ovarian cancer does not satisfy the criteria recognized by the scientific community for establishing general causation.

Opinion 2 – While I do not believe that the evidence supports the notion that there is asbestos in the cosmetic talcum powder products at issue here, the hypothetical levels of asbestos exposure from cosmetic talcum powder use proposed by plaintiffs' experts are less than or comparable to historical concentrations of asbestos present in ambient air in the US. Such low concentrations of asbestos, equal to or below those occurring in ambient air, are not associated with a risk for developing asbestos-related diseases, including ovarian cancer.

Opinion 3 – The relevant scientific literature does not support a causal relationship between fibrous talc and ovarian cancer.

Opinion 4 – The heavy metals that have been reported as constituents of cosmetic talcum powder, including but not limited to chromium, cobalt, and nickel, have not been associated with ovarian cancer in the scientific literature. Further, the general population is frequently exposed to each of these metals on a regular basis as a result of interactions with the environment (e.g., breathing air, drinking water, eating food). There is no evidence that use of cosmetic talc products would result in a dose of these heavy metals that exceeds applicable regulatory requirements or is capable of causing any cancer, let alone ovarian cancer.

Opinion 5 – None of the fragrance ingredients present in Johnson's Baby Powder or Shower to Shower has been associated with ovarian cancer. Further, these fragrance ingredients, as used in Johnson's Baby Powder or Shower to Shower, would not reach concentrations that would cause the product to be classified as an irritant, corrosive, or sensitizing, much less carcinogenic.

Opinion 6 – Plaintiffs' experts fail to consider the role of dose in their assessments of certain constituents in talcum powder, including asbestos, heavy metals, and fragrances. This is a fundamental error that is contrary to toxicological and risk assessment principles and renders their conclusions unreliable.

5.0 PRINCIPLES OF TOXICOLOGY AND RISK ASSESSMENT AND THE IMPORTANCE OF DOSE

5.1 General Causation

In order for adverse health effects to be attributed to a specific chemical or substance exposure, a valid scientific causation analysis must be performed. Causation analysis is a two-phased process involving both **General** and **Specific** causation. This report focuses on general causation.

The issue addressed in a **general causation** analysis is:

- Has the substance(s) in question been shown to cause the disease(s) in question in humans?

The objective methodology for proving general causation, as currently practiced, is a process that has undergone continual refinement over the last 150 years. Early efforts to formalize this process occurred when scientists and physicians sought to establish the causes of diseases induced by infectious agents whose presence could not easily or readily be identified with the naked eye (Evans, 1976; Yerushalmy & Palmer, 1959). A similar process was instituted in the 1960s as scientists began to focus on diseases induced by chemicals associated with the workplace, our environment, or lifestyle choices like smoking (Hill, 1965). In 1965, Sir Austin Bradford Hill proposed a set of guidelines to be considered when assessing any potential causal relationship between a substance and disease (Hill, 1965). There are nine considerations set forth by Hill:

1. *Strength* – The strength of association between the substance and disease. Hill pointed to increased mortality rates of scrotal cancer in chimney sweeps and lung cancer in cigarette smokers as high as 200 or 20 to 30 times greater than the unexposed population, respectively, as examples of a strong association between exposure and disease;
2. *Consistency* – Whether the consistency of the observed association has "been repeatedly observed by different persons, in different places, circumstances, and times." Further, whether the association has "been reached in quite a wide variety of situations and techniques" with consideration of possible confounding factors associated with a set of studies (Hill, 1965, p. 296);

3. *Specificity* – Associations that are "limited to specific workers and to particular sites and types of diseases" with no other known associations present "a strong argument in favour of causation" (Hill, 1965, p. 297);
4. *Temporality* – The timeline of exposure and disease, namely that exposure to the substance under evaluation must be demonstrated to occur prior to and with appropriate latency to disease development;
5. *Biological Gradient (Dose-Response)* – The greater the potential exposure to a substance, the greater incidence of observed disease. Hill noted that a "clear dose-response curve admits of a simple explanation and obviously puts the case in a clearer light" (Hill, 1965, p. 298). This is consistent with a fundamental principle of toxicology, "the dose makes the poison" (Klaassen, 2013 p. Inside Front Cover);
6. *Plausibility* – Is the suspected association consistent with the knowledge of biological plausibility? Plausibility is also considered as the integration of data across biological and social models, such that the association is supported by current state of knowledge regarding mechanism of action relevant to humans and disease etiology (Fedak et al., 2015);
7. *Coherence* – The causation effect "should not seriously conflict with the general known facts of natural history and biology" (Hill, 1965, p. 298);
8. *Experiment* – Hill used the example of a preventative action capable of preventing an observed association. He also noted that the "strongest support for the causation hypothesis may be revealed" through experimentation (Hill, 1965, pp. 298–299);
9. *Analogy* – Can one rely on similar or comparable evidence from a similar substance or disease?

Hill stated that any association between a substance and disease should be studied in the context of these nine considerations before the determination of a causal relationship was made. While he noted that none these considerations provides "indisputable evidence" to support or oppose causation, they serve as a guide in answering the fundamental question of likelihood of association. The process for establishing general causation according to the above discussed factors is well recognized among the scientific and medical community. The same or very similar considerations have been adopted by a number of scientific agencies, including the World Health Organization (WHO), the US Environmental Protection Agency (USEPA), and the American Conference of Governmental Industrial Hygienists (ACGIH), and scientists alike (Doll, 1984; Evans, 1976; Guidotti & Goldsmith, 1986; Hackney & Linn, 1979; Hill, 1965; IARC, 2006; Susser, 1977, 1986, 1991; USEPA, 2005; WHO, 1987). This methodology is also described in the Reference Manual on Scientific Evidence as the appropriate methodology to guide causation judgements (NRC, 2011).

Using established accepted methodology is critical in developing causal opinions to avoid faulty reasoning and conclusions.

6.0 TOXICOLOGY AND RISK ASSESSMENT

6.1 Basics of Toxicology

Toxicology is the field of science that studies the effects of toxicants on organisms. Knowledge of the dose required to elicit any effect plays a critical role in toxicological analysis. The Swiss physician and philosopher, Paracelcus (known as the Father of Toxicology), noted that "What is there that is not poison? All things are poison and nothing (is) without poison. Solely the dose determines that a thing is not a poison" (Klaassen, 2013 p. Inside Front Cover). In other words, even substances we consider to be non-toxic, such as water, can cause adverse effects or even death, at a high enough dose.

The relationship that describes an effect caused by a certain chemical exposure is known as the dose-response relationship. As noted previously, dose-response, or biological gradient, is one of the considerations for establishing causation. Typically, greater adverse effects occur at higher concentrations (doses) measured in terms of intensity, frequency and duration of exposure, whereas minimal to no effects may be observed at low concentrations. The chemical concentration at which a particular effect is first noted is known as the threshold for that chemical-induced effect.

Because the dose determines the likelihood, as well as the nature and intensity of an adverse health effect, both "safe" exposures and "toxic" exposures exist for all chemicals. To state that "there is no safe exposure level" for a substance as an argument for attempting to establish causation is unscientific. The concept of "no safe level" refers to the Linear No-Threshold (LNT) model, which was developed for ionizing radiation sources that directly mutate DNA. The LNT is based upon the assumption that there is no dose that does not elicit an effect. Under this assumption, low (relative to doses used in animal toxicity studies) exposure levels typically experienced in the human environment confer risk of tumor development that decreases linearly to zero at zero dose. A major factor in support of this model was the ease with which this model could be applied toxicologically. On a cancer dose-response curve, a straight line is drawn from the lowest statistically significant adverse response to the origin of the graph. The "steepness", or slope, of this line represents the theoretical carcinogenic potency of the chemical at low exposure levels. However, this model was developed prior to the understanding of natural processes that occur at the molecular and cellular levels to prevent and/or repair damage to DNA, proteins, and other cellular macromolecules, making the effect of the insult transient and/or reversible. These repair mechanisms have been shown to occur with genotoxic as well as non-genotoxic exposures and considerable evidence has since accumulated to show that such mechanisms work to prevent carcinogenesis at low chemical dose levels, including for heavy metals or other substances that have been classified as known human carcinogens (Clewell et al., 2019).

6.2 Proper Toxicological Risk Assessment Protocol

A risk assessment cannot be completed without information on dose. According to the USEPA, the National Research Council (NRC), and others (NRC, 1983, 2011; USEPA, 2021c), there are four sequential parts to a human health risk assessment, summarized below:

Step 1 - Hazard Identification: Examine whether a chemical has the potential to cause harm to humans, and if so, under what circumstances (based on an evaluation of results from epidemiologic, clinical, and toxicological research).

Step 2 – Dose-Response Assessment: Determine the quantitative relationship between exposure (dose) and observed adverse health effects.

Step 3 - Exposure Assessment: Once steps 1 & 2 are identified, examine what is known about the frequency, timing, and levels of contact with the chemical in the persons exposed.

Step 4 - Risk Characterization: Summary that includes two major components, Risk Characterization and Risk Estimation, which includes consideration of exposure level and data on expected effects at that exposure level.

Thus, an understanding of the dose necessary to induce a specific effect is essential to the risk assessment process. Risk can be considered proportional to both the identified hazard and exposure, such that both components are critical to determining risk.

$$Risk = Hazard \times Exposure$$

For example, a chemical may present a hazard to health in terms of reproductive toxicity or carcinogenicity, but without sufficient exposure, there is no risk to an individual or population. Similarly, one may experience substantial exposures to a substance, but if the substance is not a hazard for a certain health outcome, there is no risk for development of that specific effect or disease. With respect to talc, none of the plaintiffs' experts conduct a proper risk assessment because they perform a hazard identification (Step 1) in a flawed manner and essentially ignore dose-response (Step 2) and exposure assessment (Step 3). In particular, a specific or minimum dose of talc or any other constituent of talcum powder is never claimed to be correlated with development of ovarian cancer nor do they consider the degree of exposure to talc or any other constituent from the use of talcum powder.

With respect to exposure assessment (Step 3), it is important to note that external exposure to a substance can occur (e.g., perineal application of talc) without the occurrence of an internal dose. However, even if an internal dose does occur, it may be insufficient to result in a biological effect (USEPA, 2011). Thus, in a risk assessment, not only is it important to determine the overall exposure to a substance, it is also important to understand the extrinsic and intrinsic processes that result in an internal dose that may (or may not) reach tissues associated

with the effect under consideration. This is a critical issue associated with the hypothesis that talcum powder can induce ovarian cancer since it has not been determined how much, if any, talc or any other constituent enters into and travels through the female reproductive tract following perineal application of talcum powder. This is in part due to the absence of quantitative exposure data related to perineal application in the scientific literature as described in detail later in this report.

While qualitative exposure estimates are often used, they are ultimately not helpful in determining a causal relationship between a chemical and a disease or estimating lifetime health risks associated with exposure to a particular substance. Qualitative data collected via interviews are susceptible to recall bias, especially when the subject understands that their exposures to a substance may be associated with a disease. Additionally, qualitative data provide crude estimates (e.g., ever vs. never exposed) that are less informative in comparison with quantitative (e.g., actual measurements of concentration, frequency, and duration) or semi-quantitative data (Sullivan & Krieger, 2001; Viet et al., 2008); thus, the end result of these assessments often lacks definitive conclusions. Additionally, although a qualitative assessment indicating that an individual or group was exposed or not exposed may be useful to determine whether exposure occurred, it cannot determine whether an internal dose occurred or whether that internal dose was sufficient to cause any health effect. In sum, a meaningful conclusion from a risk assessment (Step 4) would not be possible without consideration of all the critical components discussed above.

6.3 Appropriate Dose-Response Data Sources

Data used to understand the toxic effect of a substance over a range of doses generally are derived from studies in humans (i.e., epidemiological or clinical) or laboratory animals, whereas the data generated by *in vitro* studies are typically used to identify or understand potential mechanisms of action (NRC, 2006; USEPA, 1998b; WHO, 2008).

Although there has been a desire expressed by some scientists lately to include more *in vitro* studies to reduce the use of animals for financial and ethical reasons, reliance on *in vivo* study data continues because *in vitro* experiments are not capable of modeling the complexity of the entire organism including metabolism of and immune response to foreign materials. This is important because these and other aspects of physiology can alter the response to the agent under investigation.

It is also difficult to extrapolate dose from application of a liquid suspension directly on cultured cells in a dish to an environmental concentration or an amount that might reach a distant target site following a particular *in vivo* exposure route. In other words, *in vitro* studies are often misleading in terms of plausibility due to the absence of applicable exposure route in a dish versus exposure at the target organ site. For example, if a particle elicits a toxic response in dermal cells at 500 ppm *in vitro* but these particles are too large to penetrate the outermost layer of skin (epidermis) and cannot reach the dermis upon topic application *in vivo*, then the dermis or any other internal location would not be at risk following topical dermal exposure, regardless of the concentration and amount applied to intact skin.

In the case of a chemical that is absorbed in very small amounts, modeling would be necessary to understand the external exposure dose required to equal the dose that might enter the body, then eventually reach the target tissue. According to the NRC, a considerable amount of information, including PBPK studies, human susceptibility factors, background exposures that may also affect the target tissue, and inter-individual differences among people, must be understood in order to properly interpret *in vitro* testing (NRC, 2007b). In this case, migration to and continued presence at the ovary cannot be modeled *in vitro*, regardless of the dose, and there is no direct evidence that such migration occurs *in vivo*, as discussed in greater detail in subsequent sections of this report. Thus, in the absence of additional support from animal or human studies, *in vitro* studies fail to provide adequate information from which to base risk decisions (NRC, 2007a; NRC, 2007b). Finally, it should be noted that the USEPA has indicated in its Guidelines for Carcinogenic Risk Assessment that "[d]ata from epidemiologic studies, of sufficient quality, are generally preferred for estimating risks" (USEPA, 2005).

7.0 CANCER DEVELOPMENT

The term "carcinogen" is assigned to a chemical substance or a mixture of chemical substances that are capable of causing cancer. A determination of a chemical's carcinogenic potential is generally based on evidence of the ability to induce cancer in experimental animals or increase its incidence in humans (e.g., in epidemiological studies that are well-designed and lacking significant bias). Development of cancer is a multistage and multistep process, requiring multiple sequential modifications to typical cellular processes and mutations to DNA in order to promote the uncontrolled growth of cells (Klaassen, 2013, pp. 396–398).

7.1 Multiple Stages Associated with the Cancer Development Process

The first stage in the process of cancer development is known as initiation, in which a physical or chemical carcinogen induces a genetic change (mutation or deletion event) (Klaassen, 2013, p. 397). In order for the majority of chemical carcinogens to act as initiators, they must first undergo metabolic activation inside the target cell, where the ultimate carcinogen then forms a DNA adduct, which can result in mutation. This initiating event becomes permanent in the cell if the alteration to DNA is not repaired through a suite of normal DNA repair mechanisms that continuously act to preserve the integrity of the DNA and prevent abnormal cell growth. While exogenous sources of genotoxic stress can elicit damage, endogenous threats are "constant and relentless" (Yousefzadeh et al., 2021). DNA is known to be chemically unstable under physiological conditions, and the damage and repair process occurs continuously in cells as a result of normal physiological processes and interactions. For perspective, spontaneous (unrelated to exogenous chemical exposure) DNA damage occurs at a rate of approximately 10^4–10^5 (10,000 – 100,000) events per cell per day (Lindahl, 1993; De Bont and van Larebeke, 2004, as cited by Yousefzadeh et al., 2021). Thus, it is fortunate that DNA repair mechanisms exist and initiating events rarely lead to cancer; otherwise, all humans would develop cancer early in life. The result of this is that initiation by itself is not sufficient to cause cancer. Several potential outcomes can occur following initiation: 1) the initiated cell can remain in a static nondividing state; 2) the initiated cell may possess mutations incompatible with life or normal function and cease to exist through the biological processes of cell death; or 3)

the cell (through intrinsic or chemical stimuli) divides and proliferates. Thus, not all initiated cells progress to cancerous cells.

Promotion, which is the second possible stage in the process of carcinogenesis, is "derived from either endogenous or exogenous stimuli" (Klaassen, 2013, p. 397). Promoters do not cause mutations and are generally unable to initiate tumors themselves; rather, they act through several mechanisms to increase cell proliferation or reduce controlled cell death (which would be a normal response to remove the aberrant cell) (Klaassen, 2013, p. 397). Promoters can also act through inflammation, a temporary response to damage. However, the risk of tumor growth with promoter exposure is dose-dependent and does not lead to development of tumors with low doses (Pitot et al., 1981 as cited by EWCI, 2021). Promotion requires multiple exposures and prolonged exposures are usually necessary (Bohrman, 1983). Bohrman (1983) additionally states that a promoter is not considered carcinogenic, and that exposure to the promoter must follow exposure to an initiator.

Conversion of benign pre-neoplastic lesions to neoplastic cancer is known as progression, the final stage of carcinogenesis. In this stage, cells outgrow their surrounding cells while additional genotoxic events and DNA damage may occur due to increased DNA synthesis (Klaassen, 2013, p. 398). Progression occurs spontaneously and is associated with the increased rate of cell proliferation or may occur as a result of carcinogen exposure.

7.2 Genotoxic and Non-Genotoxic Mechanisms

Carcinogens are categorized as either genotoxic or non-genotoxic, depending on their specific mechanism of action. Whereas the majority of genotoxic carcinogens are electrophiles that directly interact with and covalently bind to DNA (resulting in DNA adducts), non-genotoxic carcinogens have no direct interaction with DNA and are carcinogenic due to their ability to disrupt cellular structures and alter either the rate of cell replication or processes that increase risk of genetic error (Lee et al., 2013). Genotoxicants can cause a variety of non-cancerous mutations, which can lead to birth defects.

Genotoxic chemicals include mutagens, carcinogens and teratogens, but mutagenic and teratogenic chemicals do not necessarily cause cancer (Gregory, 2007). Chemicals that are considered mutagens can affect germ cells, which may lead to a wide variety of heritable diseases and reduced fertility (Saks et al., 2017; Wurgler & Kramers, 1992) Genotoxicants may also result in susceptibility to cardiovascular disease, including atherosclerosis, diabetes, autoimmune defects, and may be involved in aging (Wurgler & Kramers, 1992). Therefore, the fact that a chemical is considered genotoxic does not necessarily indicate that it must be carcinogenic, and vice versa. Similar to other types of toxicology studies, dose is an important factor in determining the genotoxicity of an agent.

Within the last two decades, the field of genetic toxicology has advanced from a primarily qualitative assessment of hazard without consideration of dose to a quantitative evaluation of the dose-response to allow for assessments of risk (Gollapudi, 2017; Gollapudi et al., 2013; Johnson et al., 2014). Evidence from *in vitro* and *in vivo* studies indicates that nonlinear and bilinear dose-responses exist for genotoxic effects, and there is no

significant difference in mutation frequency between the spontaneous generation in the background and following low-dose exposures with DNA-reactive agents (Klaassen, 2019, p. 503) It is now understood that cells have evolved complex processes that monitor and counteract a spontaneous ever-present level of DNA damage. The network of DNA repair pathways is reported to be ubiquitous and serves as the first line of defense for removing DNA damage and preventing mutation; these interactions of various DNA damage response and repair pathways in the cell provide biological bases for the observed threshold responses observed with genotoxic compounds (Klapacz et al., 2016). Others have stated that "[t]ogether these pathways appear sufficient to counteract mutation at low exposures/doses and/or the propagation of cells harboring significant DNA damage at least for well-studied DNA-reactive classes." (Klaassen, 2019, pp. 530–531).

In the United States, the historical default for carcinogenic risk assessment was linear extrapolation from the rodent bioassay tumor data to concentrations that were consistent with human environmental or occupational exposures (NRC, 1983, 1994; USEPA, 1986). Scientists and regulatory agencies now are beginning to revisit the linear no threshold model (Clewell et al., 2019). In 2005, the USEPA began to adopt an approach based on mechanistic data (published in *Guidelines for Carcinogenic Risk Assessment*) to inform the risk assessment process, particularly for dose-response assessment and risk characterization at low environmental exposures (Klaassen, 2013, p. 449; USEPA, 2005). In 2017, NIOSH indicated that "simple linear extraction at low doses may result in overestimation of cancer risk," further explaining that the agency's approach to future risk assessments would incorporate an evidence-based approach rather than the assumption that no chemical is safe at any dose (NIOSH, 2017).

7.3 Carcinogen Classification by Scientific Agencies

Numerous scientific and regulatory agencies evaluate epidemiological and toxicological data to classify chemicals and substances regarding their carcinogenic potential in humans. These agencies include the International Agency for Research of Cancer (IARC), the USEPA and the National Toxicology Program (NTP). Each of these agencies sets forth criteria for the evaluation and classification of substances, placing different weight on evidence from toxicological data. I have provided a brief discussion of the criteria used by select agencies for cancer classification.

7.3.1 International Agency for Research on Cancer (IARC)

IARC's evaluation of the cancer-causing ability of a chemical or substance is based upon a hazard-based analysis, which evaluates the potential for causing cancer under circumstances that do not consider exposure. As stated by IARC, "[t]he distinction between hazard and risk is important, and the [IARC] Monographs identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher" (IARC, 2006, p. 2). The distinction between hazard and risk is critical in understanding the considerations of agencies, particularly IARC, in establishing criteria for cancer classification.

In the process of evaluating carcinogenic potential, IARC reviews "openly available" epidemiologic literature, cancer bioassays in animals, and mechanistic data (IARC, 2006, p. 4). As part of the evaluation process, IARC draws conclusions based on the weight of evidence from human and animal data. Carcinogenicity in humans is classified into one of the following categories:

- ***Sufficient evidence of carcinogenicity*** – A causal relationship between the substance under evaluation and cancer in humans has been established. Specifically, "a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence" (IARC, 2006, p. 19). Included in this classification, is specification of the organ(s) or tissue(s) where the increased risk of cancer has been observed in humans;
- ***Limited evidence of carcinogenicity*** **–** Used in instances where "[a] positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias, or confounding could not be ruled out with reasonable confidence" (IARC, 2006, pp. 19–20);
- ***Inadequate evidence of carcinogenicity*** **–** An inadequacy of reliable data based on insufficient study quality, consistency, or statistical power of available studies or lack of data to allow for conclusion of the presence or absence of a causal association (IARC, 2006, p. 20);
- ***Evidence suggesting lack of carcinogenicity*** **–** Existence of "several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure" (IARC, 2006, p. 20).

Similarly, IARC classifies evidence of carcinogenicity in animals as follows:

- ***Sufficient evidence of carcinogenicity*** **–** Established based upon increased incidence of malignant neoplasms in 1) two or more species, 2) two or more independent studies in one species, or 3) in a single species in a GLP-conducted study (IARC, 2006, p. 20);
- ***Limited evidence of carcinogenicity*** **–** "[D]ata suggest a carcinogenic effect but are limited for making a definitive evaluation" based upon limitations in study design and/or interpretation of results (IARC, 2006, p. 21);
- ***Inadequate evidence of carcinogenicity*** **–** Neither presence nor absence of carcinogenicity due to major limitations constraining interpretation or lack of available data (IARC, 2006, p. 21);
- ***Evidence suggesting lack of carcinogenicity*** **–** "Adequate studies involving at least two species are available which show that … the agent is not carcinogenic" (IARC, 2006, p. 21).

In addition, the strength of evidence from mechanistic studies of carcinogenic effects is described as "weak, moderate or strong" where applicable (IARC, 2006, p. 21). IARC's overall evaluation takes into account the overall strength of the body of evidence, and categorizes a chemical or substance as follows:

- ***Group 1: The agent is carcinogenic to humans –*** Based upon sufficient evidence of carcinogenicity in humans or when evidence is less than sufficient in humans, but animal studies show sufficient evidence of carcinogenicity along with strong mechanistic evidence with relevance to human exposure;
- ***Group 2a: The agent is probably carcinogenic to humans –*** Based upon limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals. Classification may also occur in instances of inadequate evidence in humans, but sufficient evidence in animals with strong mechanistic evidence applicable in humans. Finally, limited evidence of carcinogenicity in humans alone may be sufficient for classification in Group 2a;
- ***Group 2b: The agent is possibly carcinogenic to humans –*** Based upon limited evidence of carcinogenicity in humans and less than sufficient evidence in animals. May also be used in instances of 1) inadequate evidence of carcinogenicity in humans and sufficient evidence in animals, 2) inadequate evidence in humans, less than sufficient evidence in animals, and mechanistic supportive evidence, or 3) strong evidence from mechanistic data alone;
- ***Group 3: The agent is not classifiable as to its carcinogenicity to humans –*** Most commonly used in instances of inadequate evidence for carcinogenicity in humans and inadequate or limited evidence in animals, or in cases where there is strong evidence for lack of mechanistic relevance in humans;
- ***Group 4: The agent is probably not carcinogenic to humans –*** Based on evidence suggesting lack of carcinogenicity in humans and animals. Selection for IARC review is typically based on some evidence or suspicion on cancer in the scientific literature. As a result of this selective approach for evaluation, no chemicals are currently classified under Group 4 (IARC, 2006).

7.3.2 National Toxicology Program (NTP)

The National Toxicology Program (NTP) of the U.S. Department of Health and Human Services follows a multi-step procedure to review and evaluate substances to prepare the Report on Carcinogens (RoC) (NTP, 2016). The process for listing substances includes selecting substances for evaluation, preparing draft RoC monographs for selected substances and peer reviewing and finalizing the RoC monographs, and publishing the RoC (NTP, 2016). The NTP evaluates agents, substances, mixtures, and exposure circumstances against two listing criteria to determine listing materials in the RoC:

- ***Known to be Human Carcinogen –*** NTP classifies agents as Known to Be a Human Carcinogen when "[s]ufficient evidence of carcinogenicity from studies in humans" is available, which indicates a causal relationship between exposure to the agent, substance, or mixture and human cancer (NTP, 2016).
- ***Reasonably Anticipated to be a Human Carcinogen*** – Agents are classified as Reasonably Anticipated to be a Human Carcinogen when there is "limited evidence of carcinogenicity from studies in humans," indicating a credible causal interpretation, but the evidence does not rule out alternative explanations such as chance, bias, and confounding. NTP also uses this classification when there is "sufficient evidence of carcinogenicity from studies in experimental animals," indicating "an increased incidence of malignant and/or a combination of malignant and benign tumors" either in multiple species or multiple tissues, via multiple exposure routes, or to a degree unusual for the incidence, site, tumor type, or onset

age. Materials are also classified in this group when "less than sufficient evidence of carcinogenicity in humans or laboratory animals" exists, but the agent is structurally related to a well-defined substance class which was previously listed in a RoC as either "known to be a human carcinogen or reasonably anticipated to be a human carcinogen," and additional information indicates the substance "acts through mechanisms" suggesting it would "likely cause cancer in humans" (NTP, 2016).

7.3.3 US Environmental Protection Agency (USEPA)

The USEPA uses a weight of evidence system to classify an agent's human carcinogenicity. This process evaluates the complexity of available information and considers route and extent of exposure required for cancer development. Further, the weight of evidence approach accounts for disproportionate hazards presented by age and/or genetic considerations. The USEPA employs five classifications to describe an agent's carcinogenicity to humans.

- ***Carcinogenic to Humans*** **–** This description "indicates strong evidence of human carcinogenicity" (USEPA, 2005). Agents are classified in this group when there is "convincing epidemiologic evidence of a causal association between human exposure and cancer" (USEPA, 2005). This classification is also used when there is "lesser weight of epidemiologic evidence that is strengthened by other lines of evidence," including strong evidence of exposure as a precursor but insufficient evidence to establish a causal association, substantial evidence of carcinogenicity in animals, identification of mode of action in animals, and strong evidence supporting a key precursor event to cancer response in animals that indicates occurrence in humans (USEPA, 2005).

- ***Likely to Be Carcinogenic to Humans*** **–** This classification is used "when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans," but is not sufficient to classify the substance as "Carcinogenic to Humans" (USEPA, 2005). Agents classified in this group demonstrate "a plausible (but not definitively causal) association between human exposure and cancer" in biological studies not specific to carcinogenetic animal studies (USEPA, 2005). This description is also applied to agents that may not have shown carcinogenicity in humans but demonstrate cancerous outcomes in multiple species, sexes, strains, sites, or exposure routes; raise further biological concerns; or are otherwise supported by a positive tumor study and additional lines of evidence (USEPA, 2005).

- ***Suggestive Evidence of Carcinogenic Potential*** **–** Agents are classified in this group when the weight of evidence suggests carcinogenicity and raises concern for potential human carcinogenic effects, but the evidence is "not sufficient for a stronger conclusion" (USEPA, 2005). Evidence supporting an agent in this classification may include conflicting evidence, confounding factors, limited confidence in study conclusions, and no overall dose-response trend. Additional studies on these agents may provide further insight to the agents' carcinogenicity (USEPA, 2005).

- ***Inadequate Information to Assess Carcinogenic Potential*** **—** Agents are classified in this group when the weight of evidence suggests carcinogenicity and raises concern for potential human carcinogenic effects, but the evidence is "not sufficient for a stronger conclusion" (USEPA, 2005). Evidence supporting an agent in this classification may include conflicting evidence, confounding factors, limited confidence

in study conclusions, and no overall dose response trend. Additional studies on these agents may provide further insight regarding their potential carcinogenicity (USEPA, 2005).

- ***Not Likely to be Carcinogenic to Humans –*** This classification is used when the available information is "considered robust for deciding that there is no basis for human hazard concern" (USEPA, 2005). While evidence for carcinogenicity in animals may exist for these agents, there is also "consistent evidence that each mode of action in experimental animals does not operate in humans" (USEPA, 2005). Classifying materials in this descriptor may rely upon evidence demonstrating a lack of carcinogenic effects in animals of more than one appropriate species, showing a carcinogenic effect via a specific exposure route, or otherwise indicating irrelevance to human health.

8.0 OVARIAN CANCER

The ovaries are comprised of epithelial, germ, and stromal cell types, each of which has the potential to develop into an ovarian tumor (ACS, 2018b). Germ cells are those involved with the production of the ova, and the estrogen- and progesterone-producing stromal cells originate from the connective tissue of the ovary. Germ cell tumors and stromal cell tumors are both relatively uncommon and together make up fewer than 10% of malignant ovarian carcinomas (ACS, 2018b; NCI, 2022).

The American Cancer Society (ACS) classifies epithelial tumors originating from the surface cells of the ovaries, as benign, borderline, or malignant. Benign epithelial ovarian tumors do not spread and usually do not lead to further serious illness. Borderline epithelial tumors, also known as low malignant potential tumors, differ from typical ovarian cancers in that they do not grow into the connective stromal tissue of the ovary. If borderline tumors spread outside of the ovaries, they will grow on the abdominal lining rather than into it. The ACS stated that "[borderline] tumors grow slowly and are less life-threatening than most ovarian cancers" (ACS, 2018b). Malignant epithelial ovarian carcinomas, those that are cancerous, are the most common subtype of epithelial ovarian tumor and are further subcategorized as high- or low-grade serous carcinomas, clear cell carcinomas, mucinous carcinomas, and endometrioid carcinomas (ACS, 2018b). The National Cancer Institute (NCI) reported that epithelial ovarian carcinomas are "one of the most common gynecologic malignancies" and "the fifth most frequent cause of cancer death in women" (NCI, 2023).

8.1 Risk Factors for Ovarian Cancer

8.1.1 Factors for Increased Risk of Ovarian Cancer

Familial history of the disease is one of the most significant risk factors for ovarian cancer. According to the NCI, a family history of breast and ovarian cancer can contribute to an increased risk of ovarian cancer (NCI, 2023). The American Cancer Society (ACS) also includes a family history of colorectal cancer, stating that "these cancers can be caused by an inherited mutation *(change)* in certain genes that cause a family cancer syndrome that increases the risk of ovarian cancer" (ACS, 2018a). Family cancer syndrome is associated with inherited deleterious mutations (those that increase the likelihood an individual will develop a certain disease), including

the BRCA1 and BRCA2 genes, which are the cause of most known inherited ovarian cancers, PTEN tumor hamartoma (Cowden disease), hereditary nonpolyposis colon cancer, Peutz-Jeghers syndrome, and MUTYH-associated polyposis (ACS, 2018a; NCI, 2023).

Other factors with "adequate evidence" of an increased risk of ovarian cancer are endometriosis, current or recent hormone therapy, and increases in height and body mass index (BMI) (NCI, 2019). NCI has made such determinations in part based on consistency of the reported effect across case-control and cohort studies for each factor. Factors such as endometriosis and hormone therapy have been linked with specific histologic subtypes (NCI, 2021).

8.1.2 Factors with Uncertain Risk or Inadequate Evidence of Risk of Ovarian Cancer

According to NCI, ovarian stimulation used for purposes of infertility treatment has shown inconsistent results as to associations with ovarian cancer risk. NCI also reported that women who do not become pregnant following ovarian stimulation may be at increased risk of developing ovarian cancer (NCI, 2024). In addition, diet, aspirin and nonsteroidal anti-inflammatory drug (NSAID) use, as well as perineal talcum powder exposure are factors with "inadequate evidence" for association with ovarian cancer risk based on inconsistent or lack of evidence in the available scientific literature (NCI, 2024).

IARC has stated that "sufficient evidence" is available in humans that exposure to asbestos can cause ovarian cancer (IARC, 2012b). Meanwhile, others have questioned or called for further research into any potential risk for developing ovarian cancer in response to asbestos exposure (Bunderson-Schelvan et al., 2011; Camargo et al., 2011; Reid et al., 2011; Slomovitz et al., 2021). IARC's evaluation and classification of the association between asbestos and ovarian cancer is discussed in more detail later in my report.

8.1.3 Factors for Decreased Risk of Ovarian Cancer

According to the NCI, the use of oral contraceptives, multiparity and multiple pregnancies, breastfeeding, tubal ligation, and salpingectomy (removal of fallopian tube) are factors that are associated with a decreased risk of developing ovarian cancer (NCI, 2024). In a review of epidemiology studies for ovarian cancer, Reid et al. (2017) stated that "[i]t is well established that among high risk women, bilateral prophylactic oophorectomy decreases risk by at least 90%," and "[n]umerous studies have identified a reduced risk associated with either a hysterectomy or tubal ligation ranging from 30-40% with the highest risk reductions observed among endometrioid and clear cell histotypes" (Reid et al., 2017). The authors also reported that "parous women have a 30-60% lower risk than nulliparous women and each additional full-term pregnancy lowers risk by approximately 15%" (Reid et al., 2017, p. 13).

9.0 TALC

9.1 Overview of Cosmetic Talc

Talc is a hydrated silicate mineral consisting of magnesium, silica, oxygen and water with the chemical formula $Mg_3Si_4O_{10}(OH)_2$. The term talc may also refer to rock, ore, or a commercial product containing the mineral talc. Talc is used in a variety of applications and products as an anti-sticking agent, absorbent, pigment, lubricant, thickener, carrier, and filler (IARC, 2010). Over the past century, talc has been produced from mines throughout the United States and worldwide (Chidester et al., 1964; IARC, 2010). The geological conditions under which a talc deposit is formed contribute to the unique mineral composition and morphology of the talc. Hence, talc produced from different geographical locations may possess distinct variations in these properties (Van Gosen et al., 2004a, 2004b). Talc is generally classified into two commercial grades: cosmetic and industrial. These grades refer to the relative purity and suitability of talc for various applications based on the inherent physical properties of the mined product. Other considerations include color, particle size and morphology, and presence of associated minerals.

Cosmetic talc consists of a high purity product (>95-99 percent) consisting of platiform or platy particles (ACGIH, 2010). Platy refers to a mineral particle shape consisting of one short (i.e., thickness) and two longer dimensions (i.e., length and width) (Campbell et al., 1977). In the case of talc, platy particles are arranged into planed sheets held together by weak forces. These thin plates and sheets overlap and slide across one another readily. The physical properties of platy talc contribute to the desired characteristics of use in cosmetic products, including softness of feel, lubricity, and ease of application. Therefore, only high purity platy talc has been historically used in the cosmetic industry (Zazenski et al., 1995). Consumer uses of talc include loose formulations of baby and body powders, antiperspirants, and make-up products including lipstick, eye shadow, and foundations (Zazenski et al., 1995).

As part of the evaluation of the question of general causation (can a substance cause a disease?), I have considered the wide breadth of literature concerning cosmetic talc and cancer. This includes literature examining the association of cosmetic talc and ovarian cancer based on: 1) epidemiology studies of those exposed to cosmetic talc via occupational and consumer use scenarios, 2) studies of experimental animals exposed to cosmetic talc via multiple routes of administration, and 3) cellular and/or mechanistic studies conducted *in vitro*. These studies are summarized in the following sections.

10.0 HUMAN EPIDEMIOLOGICAL STUDIES OF TALC AND OVARIAN CANCER

The potential for cosmetic talc to induce cancer, including ovarian cancer, in humans has been evaluated in numerous epidemiology studies. Significant positive associations between exposure and disease in well-conducted epidemiological studies are considered strong lines of evidence for understanding human risk (NRC, 1983). Two types of epidemiology studies – case-control and cohort – have been used to investigate a possible association between perineal exposure to cosmetic talcum powder and the development of ovarian cancer.

These study types are primarily distinguished in terms of design, population selection and timeframe of exposure classification. For example, cohort studies are prospective in nature, beginning with a group of initially disease-free individuals who are followed over time for development of disease. Based on exposure status among individuals within the study population, statistical methodologies are applied to estimate risk of developing disease. Meanwhile, case-control studies involve individuals selected based on their disease status, who are then matched with disease-free controls. Exposure histories are compared across the case and control groups to identify any consistent features. Case-control studies, by contrast, are retrospective; exposure and health outcomes among study participants have already occurred. While each study presents unique advantages and disadvantages, it is generally accepted that cohort studies carry greater weight for purposes of risk evaluation. In particular, the retrospective nature of case-control studies leads to greater susceptibility to bias.

10.1.1 Talc Mining and Milling Cohorts and Respiratory Disease

A significant body of literature exists regarding respiratory cancers among cosmetic talc mining and milling cohorts in the US and Europe. These cohorts are comprised of all or nearly exclusively male subjects, thus offering limited information relevant to ovarian cancer. However, the high levels of exposure observed in occupational settings provide important information in the general evaluation of the carcinogenic potential for talc along with dose-response considerations. In general, these studies have observed excess mortality from non-malignant respiratory disease (NMRD) in many cohorts, but limited evidence for mortality attributable to cancer (Ciocan et al., 2021; Coggiola et al., 2003; Fordyce et al., 2019; Pira et al., 2017; Rubino et al., 1979; Selevan et al., 1979; Wergeland et al., 1990, 2017; Wild et al., 2002).

A mortality study of Italian talc miners and millers of talc "recognized to be of the highest grade standard of purity" found an increase in deaths attributable to NMRD among miners, but concluded that there was no evidence of carcinogenicity (Rubino et al., 1976). Subsequent updates with up to 74 years of follow-up have found no increased cancer mortality among workers (Ciocan et al., 2021; Coggiola et al., 2003; Pira et al., 2017; Rubino et al., 1979). In a recent meta-analysis, Ciocan and colleagues reported a slight increased risk for lung cancer mortality (SMR=1.42, CI 95% 1.07-1.89) but were not able to evaluate mesothelioma due to the small number of studies overall. However, the authors noted that the small excess in lung cancer mortality may be due to the high prevalence of smokers in the cohorts (Ciocan et al., 2022). Additional studies of mortality and cancer risk have been examined in cosmetic talc mining and milling cohorts from Norway (Wergeland et al., 1990, 2017), France and Austria (Wild et al., 2002), and Vermont (Fordyce et al., 2019; Selevan et al., 1979). A significant excess of NMRD and respiratory cancer mortality was reported by Selevan et al. (1979), although occupational exposure to radon and other non-talc minerals may have been contributing factors. In a recent update of the Vermont talc worker cohort, one case of mesothelioma, which could not be attributed to talc exposure from the mine, was identified with no evidence of increased mortality due to cancer (Fordyce et al., 2019).

10.1.2 Other Occupational Talc Exposures and Cancer

Other cohort and case-control studies have examined workers exposed to talc in ceramic, pulp and paper, and rubber manufacturing industries (Bulbulyan et al., 1999; Langseth & Andersen, 1999, 2000; Langseth & Kjærheim, 2004; Straif et al., 1999, 2000; Thomas & Stewart, 1987; Zhang et al., 1989). While these studies found varying instances of increased risk to cancers, they generally contained incomplete information regarding the nature, duration, and frequency of talc exposure. Additionally, the jobs examined in these studies are associated with other occupational exposures – silica, wood dust, microorganisms, asbestos, and carbon black – or smoking history. These additional considerations make it difficult to interpret any potential associations with talc exposure among these occupational studies.

More recently, Lewis et al. (2023) investigated occupational exposure of barbers, hairdressers, and cosmetologists to cosmetic talc and its potential link to mesothelioma. The authors carried out a systematic review of the literature, ultimately narrowing to 12 available epidemiological studies for detailed review. In addition, these studies were supplemented with data drawn from occupational mortality databases managed by the Washington State Department of Health and NIOSH for 26 U.S. states. According to the authors, their analysis of the various epidemiological studies revealed no link between talc exposure inherent to work as barbers, hairdressers, or cosmetologists and mesothelioma. In most investigations, associations with profession or estimated exposure were null, though significant associations observed in some studies were primarily inverse, indicative of a protective rather than causal effect. The Washington Department of Health database did report an increased risk of peritoneal and pleural malignancies among select age-groups of female barbers, hairdressers and cosmetologists, yet the total number of deaths among these groups was 4, and therefore must be interpreted cautiously. The authors noted large variation in study methodologies, talc formulations, and average durations of exposure across the included data sources. However, despite these variations, the authors concluded that “the consistency of the results reported in the epidemiological literature and as supplemented with the PMR queries, combined with the breadth of geography, timeframe, study design, and research groups encompassed by these data, suggest that our systematic review is likely representative of the epidemiology on this topic”.

10.1.3 Occupational Cohorts and Case-Controls Specific to Ovarian Cancer

A limited number of cohort studies have examined the associations between occupational exposure to talc and ovarian cancer. In 1992, Chen et al. reviewed risk factors for epithelial ovarian cancer among a group of 112 women diagnosed with epithelial ovarian cancer living in Beijing, China between 1984 and 1986. Also included were 224 aged-matched community controls. The authors noted that there were seven women diagnosed with ovarian cancer and five women in the control group who reported using dusting powder on the lower abdomen and perineum for at least three months (RR: 3.9; 95% CI: 0.9 – 10.6). It was noted that other sources of exposure may also bring talc into the pelvic cavity, including abdominal surgery, pelvic examinations (through medical gloves), and occupational exposures. The authors stated that “[t]he small number of women who used dusting powder (seven cases and five controls) makes it impossible to distinguish among the types of exposures” (Chen

et al., 1992). Occupational exposures to talc were also reported in association with ovarian cancer (RR: 0.9; 95% CI: 0.3 – 2.9). This study was limited by the small population and lack of information regarding talc application practices.

A 1994 case-control study reviewed the work histories of 296 Washington, DC area women aged 20 to 29 who were potentially occupationally exposed to talc and diagnosed with epithelial ovarian cancer from 1978 to 1981. The women were compared to 343 women discharged from the same Washington, DC area hospitals for unrelated conditions. The most common job titles reported by both groups of women were secretary, teacher, nurse, and cleaner (housekeepers and custodians). A blind exposure assessment examined the relative risk of ovarian cancer according to the length of exposure to talc. Five women diagnosed with ovarian cancer and 11 women in the control group reported less than five years of occupational exposure to talc (RR: 0.5; 95% CI: 0.1 – 1.4). Two women diagnosed with ovarian cancer and eight women in the control group reported between five and nine years of occupational exposure to talc (RR: 0.3; 95% CI: 0.1 – 1.4). Five women diagnosed with ovarian cancer and 12 women in the control group reported at least ten years of occupational exposure to talc (RR: 0.5; 95% CI: 0.2 – 1.5). The authors reported that "women exposed to talc had a relative risk of ovarian cancer below the null, but the confidence interval was wide and there was no evidence of a trend" (Hartge & Stewart, 1994). The authors noted that "no indication of occupational hazard for ovarian cancer was seen in these data," which was attributed to the assumption of homogeneity or the small study size (Hartge & Stewart, 1994). There was also no reference as to the nature of the reported talc exposure.

Langseth and Kjaerheim (2004) conducted a case-control study of female pulp and paper workers (46 cases and 184 controls) from 11 mills in Norway to examine the association between talc exposure and risk of ovarian cancer (Langseth & Kjærheim, 2004). The women in this study were also exposed to asbestos and total dust as part of their occupations. The authors found an odds ratio of 1.10 (95% CI: 0.56 – 2.18) for women who were ever occupationally exposed to talc. The authors concluded that women who were occupationally exposed to talc did not have an increased risk of ovarian cancer.

Leung et al (2023) performed a case-control study which investigated the relationship between occupational history and ovarian cancer in Montreal, Canada from 2011 to 2016. The study population consisted of 491 newly diagnosed epithelial ovarian cancer (EOC) cases and 897 frequency-matched controls drawn from the population-based The Prevention of Ovarian Cancer in Quebec (PROVAQ) study; participants were required to have been employed in a job for at least six months outside the home, and exposure history was estimated using the Canadian job-exposure matrix (CANJEM). When modeling the odds of EOC for specific professions and controlling for demographic covariates, the authors observed statistically significant elevated ORs for accountants (OR=2.05, 95% CI: 1.10, 3.79); hairdressers, barbers, beauticians, or related professions (OR=3.32, 95% CI: 1.25, 8.27); retail trade (OR=1.59, 95% CI: 1.05, 2.39); and construction (OR=2.79, 95% CI: 0.52, 4.83). Elevated ORs were also observed for sewers and embroiderers (OR=1.85, 95% CI: 0.77, 4.45) and salespeople, shop assistants and demonstrators (OR=1.45, 95% CI: 0.71, 2.96), though these associations were not statistically significant. Additionally, associations were observed for high cumulative exposure to 18 agents (including cosmetic talc and various others). This study had relatively low power to examine associations with uncommon professions – and potentially linked exposures – however, and the potential for residual confounding due to

lacking information on several covariates. Further, the authors did not control for multiple testing, so some associations may have been due to chance.

Saito (2022) conducted a retrospective ecological mortality study of asbestos-related diseases which included mesothelioma, asbestosis, and pleural plaques in Brazil between 2000 and 2017 for individuals over 30 years old. The authors additionally examined lung and ovarian cancers obtained from one Health Information Service (HIS). Health outcome data was obtained from Brazilian mortality information system, public and private hospital admission databases, hospital cancer registries from the National Cancer Institute (INCA), and the compulsory disease notification system. Disease records were recorded with ICD-10 codes and ICD-O-3 in the INCA database. Population data was from the Brazilian 2000 and 2010 census data. High consumption areas for asbestos were identified as a total of 29 municipalities with either asbestos mining or asbestos-cement plants and compared to the rest of the Brazilian municipalities as a reference group. A total of 2,721 pooled asbestos disease-related deaths, 419,265 deaths for lung cancer, and 58,182 ovarian cancer deaths records between 2000 and 2017 were found. Saito and colleagues reported that the standardized rate ratio for ovarian cancer as 1.34 (95% CI: 1.31-1.37).

10.1.4 Consumer Exposure to Talc and Ovarian Cancer

A number of epidemiology studies have been conducted over the past several decades that have investigated the risk of developing ovarian cancer in association with use of cosmetic talc-containing products including talcum powders. The available case-control and cohort studies vary in terms of data quality and consideration of potential confounding factors. In addition, a number of pooled studies and meta-analyses have assessed potential risk factors for ovarian cancer, including talcum powder use.

- **Case-Control Studies**

A number of case-control studies have evaluated whether there is an association between perineal or general cosmetic talc use and ovarian cancer (Booth et al., 1989; Chang & Risch, 1997; Chen et al., 1992; Cook et al., 1997; Cramer et al., 1982, 2005, 2016; Cramer & Xu, 1995; Davis et al., 2021; Eltabbakh et al., 1998; Gates et al., 2008; Godard et al., 1998; Green et al., 1997; Harlow et al., 1992; Hartge et al., 1983; Kurta et al., 2012; Langseth & Kjærheim, 2004; Moorman et al., 2009; Rosenblatt et al., 1992, 2011; Schildkraut et al., 2016; Tzonou et al., 1993; Whittemore et al., 1988; Wu et al., 2009, 2015). While I do not discuss each specific case-control study individually in this report, a brief summary of data and findings for each study can be found in **Appendix C** as well as in **Tables 1 and 2**, below. I have also summarized the available cohort studies, as well as recent meta-analyses and reviews which have analyzed the various case-control studies.

Table 1: Characteristics of Case-Control Studies Examining the Association Between Consumer Talc Exposure and Ovarian Cancer

Reference	Study Type	Country	# Cases (Controls)	Potential Confounders Controlled For									
				Parity	Gravidity	Menopause	Hysterectomy	Tubal Ligation	Age	Oral Contraceptive	Weight	Smoking	Family History
Cramer et al. (1982)	P	US	215 (215)	X	X				X	X	X	X	
Hartge et al. (1983)	H	US	135 (171)						X				
Whittemore et al. (1988)	H, P	US	188 (539)[a]							X[f]			
Booth et al. (1989)	H	UK	235 (451)						X				
Chen et al. (1992)	P	China	112 (224)										
Harlow et al. (1992)	P	US	235 (239)	X					X		X		
Rosenblatt et al. (1992)	H	US	77 (46)	X							X		
Tzonou et al. (1993)	H	Greece	189 (200)	X	X				X		X	X	
Cramer and Xu (1995)	P	US	450 (454)										
Chang and Risch (1997)	P	Canada	450 (564)			X	X	X	X	X			X
Cook et al. (1997)	P	US	313 (422)						X				
Green et al. (1997)	P	Australia	824 (855)	X	X	X			X	X	X	X	X
Eltabbakh et al. (1998)	H	US	503 (50)[c]										
Godard et al. (1998)	P	Canada	170 (170)										
Ness et al. (2000)	P	US	767 (1,367)			X	X	X	X	X			X
Langseth and Kjaerheim (2004)	P	Norway	19 (95)										
Mills et al. (2004)	P	US	256 (1,122)						X	X			
Cramer et al. (2005)	P	US	668 (705)						X				
Gates et al. (2008)	P	US	1,385 (1,802)	X				X	X	X	X		
Merritt et al. (2008)	P	Australia	1,576 (1,509)						X	X			
Moorman et al. (2009)	P	US	143 (189)[d]						X				
			943 (868)[e]						X				
Wu et al. (2009)	P	US	609 (688)			X		X	X	X			X
Rosenblatt et al. (2011)	P	US	812 (1,313)						X				
Kurta et al. (2012)	P	US	902 (1,802)						X				

Reference	Study Type	Country	# Cases (Controls)	Potential Confounders Controlled For									
				Parity	Gravidity	Menopause	Hysterectomy	Tubal Ligation	Age	Oral Contraceptive	Weight	Smoking	Family History
Wu et al. (2015)	P	US	1,701 (2,391)	X					X		X		
Cramer et al. (2016)	P	US	2,041 (2,100)	X					X	X	X		
Schildkraut et al. (2016)	P	US	584 (745)	X		X		X	X	X	X		X
Davis et al. (2021)	P[f]	US	3,420 (7,881)	X	X	X	X	X	X	X	X	X	X
Gabriel et al. (2019)	P	US	2,040 (2,100)	X		X		X	X	X	X	X	

P = Population-based

H = Hospital-based

[a] 188 hospital-based cases, 280 hospital-based controls, 259 population-based controls

[b] Only for mode of exposure

[c] Controls were diagnosed with primary peritoneal cancer. Healthy controls were not enrolled

[d] African American cases and controls

[e] Caucasian cases and controls

[f] Pooled case-control study based on four case-control studies and one nested case-control study in the Ovarian Cancer in Women of African-American Ancestry consortium

Table 2: Findings from Case-Control Studies Examining the Association Between Consumer Talc Exposure and Ovarian Cancer

Reference	Mode of Exposure and RR (95% CI)				Extent of Use		
	Any	Perineum Dusting	Sanitary Napkin	Diaphragm	Frequency	Duration	Total Applications
Cramer et al. (1982)	**1.92 (1.27-2.89)[a]**						
	1.61 (1.04-2.49)[a]						
Hartge et al. (1983)	0.7 (0.4-1.1)[b]	2.5 (0.7-10.0)[c]		0.8 (0.4-1.4)			
Whittemore et al. (1988)	1.36 (0.91-2.04)[d]	1.45 (0.81-2.60)	0.62 (0.21-1.80)	1.50 (0.63-3.58)	p = 0.19	p = 0.61	
Booth et al. (1989)	1.3 (0.8-1.9)[e]			NA[f]	p = 0.05		
Chen et al. (1992)		3.9 (0.9-10.63)					
Harlow et al. (1992)	1.5 (1.0-2.1)[g]	**1.7 (1.1-2.7)[g]**	1.1 (0.4-2.8)[g], [h]	1.2 (0.6-2.4)[g]	**p = 0.046**	p = 0.07	**p = 0.015**
Rosenblatt et al. (1992)		1.7 (0.7-3.9)[g]	**4.8 (1.3-17.8)[g]**	3.0 (0.8-10.8)[g]			
Tzonou et al. (1993)		1.05 (0.28-3.98)					
Cramer and Xu (1995)	**1.6 (1.2-2.1)**						
Chang and Risch (1997)	**1.42 (1.08-1.86)[g]**	1.312 (1.00-1.73)[g]	1.26 (0.81-1.96)[g]		0.89 (0.74-1.07)[g]	1.091 (0.98-1.21)[g]	
Cook et al. (1997)	1.2 (0.6-2.5)						
Green et al. (1997)		**1.3 (1.1-1.6)**				No trend obs.	
Eltabbakh et al. (1998)							**p = 0.003**
Godard et al. (1998)		2.49 (0.94-6.58)					
Ness et al. (2000)		**1.5 (1.1-2.0)[g]**	**1.6 (1.1-2.3)[g]**	0.6 (0.3-1.2)[g]		1.2 (1.0-1.5)[g],[i]	
Langseth and Kjaerheim (2004)	1.15 (0.41 – 3.21)[g]						
Mills et al. (2004)	**1.37 (1.02-1.85)[g]**				**p = 0.015**	**p = 0.045**	p = 0.051
Cramer et al. (2005)		1.16 (0.90-1.49)[g]					
Gates et al. (2008)		**1.36 (1.14-1.63)**			**p = < 0.001**		
Merritt et al. (2008)		**1.17 (1.01-1.36)[g]**				**p = 0.021**	
Moorman et al. (2009)	1.19 (0.68-2.09)[g]						
	1.04 (0.82-1.33)[g]						
Wu et al. (2009)	**1.48 (1.15-1.91)**	**1.53 (1.13-2.09)**	1.61 (0.93-2.78)[j]	1.14 (0.46-2.87)[k]	**p = 0.032[l]**		**p = 0.0004**
Rosenblatt et al. (2011)		1.38 (0.77-2.47)[g]					
		1.27 (0.97-1.66)[g],[m]	0.82 (0.58-1.16)[g],[m]	0.72 (0.48-1.10)[g][m]		No trend obs.	No trend obs.

Reference	Mode of Exposure and RR (95% CI)				Extent of Use		
	Any	Perineum Dusting	Sanitary Napkin	Diaphragm	Frequency	Duration	Total Applications
Kurta et al. (2012)		**1.40 (1.16-1.69)**[g]					
Wu et al. (2015)		**1.46 (1.27-1.69)**[g]				**1.14 (1.09-1.20)**[g],[n]	
Cramer et al. (2016)	**1.30 (1.12-1.52)**[g],[o]	**1.42 (1.04-1.96)**[g]		0.73 (0.57-0.93)[g]	**p = < 0.0001**	**p = 0.002**	**p = 0.02**
Schildkraut et al. (2016)	**1.39 (1.10-1.76)**[g][o][m]	**1.44 (1.11-1.86)**[g],[m]			**p = < 0.01**	**p = 0.02**	**p = < 0.01**
Davis et al. (2021)		**1.32 (1.17-1.48)**[g]			p = 0.98	p = 0.97	
Gabriel et al. (2019)	**1.28 (1.09-1.51)**						**p = 0.002**

Bold = Statistically significant

[a] As a perineum dusting powder or on sanitary napkins

[b] As a body powder or on a diaphragm

[c] On genitals, sanitary napkins, or underwear; It was noted that the small number of women exposed in this manner yielded an unreliable estimate

[d] Any two of perineum dusting or on sanitary napkin or diaphragm

[e] Daily use

[f] No significant difference between cases and controls

[g] Odds ratio

[h] On sanitary napkins and/or underwear

[i] Duration of use: ≥ 10 years

[j] Use on underwear reported separately at 1.71 (0.99-2.97)

[k] Use on a diaphragm or cervical cap

[l] Frequency and duration were reported together

[m] For use with any genital powder (talc, baby powder, cornstarch, deodorant, body/bath, or other/unknown)

[n] Per five years of talc use

[o] Personal body and genital use

Among the numerous case-control studies that have examined the potential association between perineal talc use and risk of ovarian cancer, findings have been varied and inconsistent when determining potential risk and the significance of those findings. For example, of the 29 case-control studies reviewed, 17 studies (57%) reported a significant positive association between any talc use and ovarian cancer (Chang & Risch, 1997; Cramer et al., 1982, 2016; Cramer & Xu, 1995; Davis et al., 2021; Gabriel et al., 2019; Gates et al., 2008; Green et al., 1997; Harlow et al., 1992; Kurta et al., 2012; Merritt et al., 2008; Mills et al., 2004; Ness et al., 2000; Rosenblatt et al., 1992; Wu et al., 2009, 2015). One of these studies only found a statistically significant association for talc use on sanitary napkins (Rosenblatt et al., 1992). Another study (Schildkraut et al., 2016) reported a statistically significant association for use with genital powder generally and did not report specifically about perineal talc use. Of the 19 case-control studies that specifically examined perineal talcum powder use, 10 (53%) reported a statistically significant positive association with ovarian cancer (Cramer et al., 2016; Davis et al., 2021; Gates et al., 2008; Green et al., 1997; Harlow et al., 1992; Kurta et al., 2012; Merritt et al., 2008; Ness et al., 2000; Wu et al., 2009, 2015), while nine did not find a statistically significant association (Chang & Risch, 1997; Chen et al., 1992; Cramer et al., 2005; Godard et al., 1998; Hartge et al., 1983; Rosenblatt et al., 1992; Tzonou et al., 1993; Whittemore et al., 1988).

In addition, a number of the case-control studies do not account for, or contain incomplete information regarding, the frequency and duration of talc exposure and/or potential dose, important concepts when evaluating whether or not exposure to a substance may cause or contribute to an adverse health outcome. Overall, there was limited evidence of a dose-response relationship observed among case-control studies. Of the 29 case-control studies reviewed, 14 reported on frequency and/or duration of use or total applications of talc use. Of those, eight (57%) found a significant trend when examining at least one parameter (Cramer et al., 2016; Eltabbakh et al., 1998; Gates et al., 2008; Harlow et al., 1992; Merritt et al., 2008; Mills et al., 2004; Wu et al., 2009, 2015). Of the 11 case-control studies that found a statistically significant association between perineal talc use and ovarian cancer, nine studied frequency and/or duration of use and six of those reported significant trends (Cramer et al., 2016; Gates et al., 2008; Harlow et al., 1992; Merritt et al., 2008; Wu et al., 2009, 2015). But only two studies found a statistically significant trend when examining both parameters (Cramer et al., 2016; Wu et al., 2009). One study that reported on genital powder use (including talc among other powders) found both a statistically significant association with genital powder use and a statistically significant dose-response association (Schildkraut et al., 2016).

It should also be noted that among the various case-control studies, some study participants overlap, or potential overlap exists. Cramer and Xu (1995) is a combined study of Cramer et al. (1982) and Harlow et al. (1992). In their combined study, Cramer et al. (2016) included Gates et al. (2008) as one of their three enrollment phases. Schildkraut et al. (2016) and Davis et al. (2021) both obtained study participants from the African American Cancer Epidemiology Study.

Case-control studies have several advantages, including the ability to review multiple risk factors and the ability to obtain results relatively quickly as the identified health outcome has already occurred. This is especially useful

when examining diseases with longer latency periods. However, the retrospective nature of case-control studies also creates limitations, mainly the existence of recall bias. Recall bias is the tendency of study participants who have been diagnosed with the disease being studied to recall exposure to potential or alleged causes of that disease at a greater rate than study participants who have not been diagnosed with the disease. For example, O'Brien (2023) reported evidence of recall bias for genital talc use among women with ovarian cancer . Additionally, Schildkraut et al. (2016) demonstrated that an observed association between talcum powder use and ovarian cancer was dependent on whether the participants were interviewed before or after 2014, possibly due to increased media coverage of talc litigation.

The case-control studies that examined the potential associations between talc and ovarian cancer also exhibited inconsistency in terms of adjusting for potential confounders. In particular, a number of these studies did not adjust for certain known or suspected risk factors of ovarian cancer, including age, weight, family history, and reproductive system considerations. In an umbrella review of the literature regarding the risk factors for ovarian cancer, Wheelan (2022) explicitly state that case-control studies are susceptible to recall bias and therefore excluded them from their study entirely. They noted that they did not consider the evidence of association as robust, which is supported by the pooled analysis conducted by O'Brien (2020). Furthermore, Goodman (2024) recently performed a quantitative bias analysis of case-control studies of perineal talc use and ovarian cancer using the sensitivity and specificity information previously reported (Goodman et al., 2024) . Goodman et al found that recall bias typically results in a bias away from the null, and therefore it is likely that bias has affected other case-control studies in similar manners.

Based on these characteristics of case-control studies, the data and findings should be evaluated in the context of the greater body of scientific literature, including cohort studies, review and meta-analyses, other exposure studies, and government and scientific agency reviews, along with available toxicology and mechanistic data.

- **Cohort Studies**

The Nurses' Health Study, a prospective cohort, enrolled 121,700 registered nurses in 1976. Follow-up questionnaires were mailed to study participants every two years. Data regarding use of talcum powder, baby powder, or deodorizing powder (e.g., ever having used and frequency of use in the perineal area or on sanitary napkins) began in 1982 and was assessed in 78,630 of the study participants through 1996. The authors excluded study participants from their analysis who did not respond to the question regarding talc use in 1982 and those with a history of cancer (except for non-melanoma skin cancer) before 1982, bilateral oophorectomy (or surgery that removed an unknown number of ovaries), and radiation therapy. The authors updated their exclusions every two years. The authors found 307 cases of epithelial ovarian cancer diagnosed between 1982 and 1996. No overall association between participants who reported ever-talc use and epithelial ovarian cancer was observed (RR: 1.09; 95% CI: 0.86 – 1.37). Additionally, no increased risk was found among women who reported daily perineal use, no trend was observed with increasing frequency of use, and the use of talc-dusted sanitary napkins was inversely associated with ovarian cancer, although this relationship was not statistically significant. It should be noted that the authors did observe a modest increase in risk among women who had ever used talc

and serous invasive cancers (RR: 1.40; 95% CI: 1.02 – 1.91). Limitations acknowledged by the authors included the lack of information regarding age at first talc use and duration of use since the questionnaire only referred to ever use of talc (Gertig et al., 2000).

In 2010, Gates et al. performed a follow-up of the Nurses' Health Study (follow-up through 2006). No statistically significant association between talc users and epithelial ovarian cancer was observed overall. The authors also found a non-significant association between talc use and mucinous cancers but did not find an increased risk between talc use and any other histologic subtype, including serous cancer as previously reported by Gertig et al. (2000). The women did not provide further information about talc use after 1982. The authors stated that limitations of the study included the potential for incomplete exposure data and misclassification (Gates et al., 2010).

A 2014 review of the Women's Health Initiative Observational Study, a cohort study of 61,576 postmenopausal women enrolled from 1993 to 1998, assessed the association between perineal talc use and ovarian cancer risk. For their review, the authors excluded study participants with a history of bilateral oophorectomy (or an unknown number of ovaries at baseline) and any type of cancer (except non-melanoma skin cancer) and if any exposure or follow-up data was missing. While the Nurses' Health Study was limited by a lack of information on duration of use, the Women's Health Initiative Observational Study did collect this information. Study participants were questioned whether they had ever used powder in their genital area; those who replied in the affirmative were further questioned about the duration of use. Similar questions were asked regarding powder use on a diaphragm or sanitary napkin. Study participants underwent follow-up until diagnosis of ovarian cancer, death, loss to follow-up, or September 17, 2012, whichever came first. The mean follow-up time for study participants was 12.4 years. The authors found that ever having used perineal talc was not associated with ovarian cancer risk (HR_{adj}: 1.06; 95% CI: 0.87 – 1.28). The authors also reported that use of talc-dusted sanitary napkins (HR_{adj}: 0.95; 95% CI: 0.76 – 1.20) and diaphragms (HR_{adj}: 0.92; 95% CI: 0.68 – 1.23) was not associated with ovarian cancer risk nor was there any association with duration of perineal talc use. Limitations in the analysis included the potential for misclassifying exposures, and a lack of information regarding frequency of talc use (Houghton et al., 2014).

The Sister Study, a cohort established in 2003 that enrolled 50,884 women in the United States and Puerto Rico who had a sister diagnosed with breast cancer, investigated the association between perineal talc use and ovarian cancer risk. The authors excluded study participants with a history of bilateral oophorectomies or ovarian cancer prior to enrollment and those with no follow-up information, resulting in 41,654 women in their analysis. Study participants answered questions regarding their reproductive history, health conditions, and lifestyle and completed a questionnaire regarding the frequency of douching and talc use (applied to sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area) during the 12 months prior to enrollment. Follow-up (annual health update and questionnaire) was performed from baseline until diagnosis with ovarian cancer. The authors reported 154 cases of ovarian cancer as of July of 2014 with a median follow-up of 6.5 years. The authors found a positive association between douching and ovarian cancer (HR_{adj}: 1.84; 95% CI: 1.2 – 2.8) and

no association (slight reduction) of risk when examining ovarian cancer incidence and talc use (HR_{adj}: 0.73; 95% CI: 0.44 – 1.2) (Gonzalez et al., 2016).

Chang et al., 2024 recently utilized the Sister Study to investigate the relationship between personal care products (PCPs) mixtures and the incidence of hormone-sensitive breast, ovarian, and uterine cancers. Participants were enrolled between 2003 and 2009 and took part in periodic follow-up for 11.6 years on average. Detailed information on demographic characteristics and the use of 41 PCPs over the previous 12 months was collected through questionnaires at baseline. PCPs included "12 beauty products, …seven everyday hair products, …eight hygiene products [including talc: underarm, genital, and other areas], …and 14 skincare products" (p. 2). Analyses for each cancer type were restricted to women with complete survey and follow-up, no cancer diagnoses at baseline, and no procedures at baseline that would restrict possible cancer development (i.e., oophorectomies or hysterectomies). The authors reported a hazard ratio of 1.35 (95%CI: 1.00, 1.83) between hygiene mixtures and ovarian cancer. However, when analyzed by the individual PCP, the authors observed no significant association between individual PCPs and the development of ovarian cancer. Inverse associations were observed for all talc applications, whether under-arm (HR=1.05, 95%CI=0.93, 1.19), vaginal (HR=1.04, 95% CI: 0.91, 1.19), or other sites (HR=0.98, 95% CI: 0.88, 1.09), though these associations were not significant after adjustment for multiple comparisons. Consequently, despite the bias potential of self-reported PCP data, these opposing trends lend substantial uncertainty to the link between talc-containing PCPs' and development of hormone-sensitive cancers.

O'Brien et al., 2024, performed an additional analysis on the Sister Study cohort, but used results from a retrospective follow-up questionnaire (2017-2019). After combining this retrospective data with predicted results for cohort members who did not answer the follow-up questionnaire (approximately 27 percent), the authors reported a statistically significant increased risk of ovarian cancer from talc use (HR=1.82, 95%CI=1.36, 2.43). This result, based in part on predictive, rather than real, data, is an outlier. Moreover, the real data that were collected came from a questionnaire given in 2017-2019, raising very obvious concerns about recall bias. I defer to other experts on whether and to what extent O'Brien et al. adjusted for this bias, or whether any such adjustment would have been sufficient. However, given the obvious questions surrounding data collection, and the incongruity of the results with the rest of the literature, this study does not change my analysis (O'Brien et al., 2024).

As discussed with respect to the case-control studies, above, the cohort studies did not all adjust for the same confounders. Cohort studies are also potentially limited by the length of follow-up periods and/or loss of follow-up among study participants especially when examining diseases with long latency periods. Nonetheless, these cohort studies exhibit consistency in finding no evidence of any association between talcum powder use and ovarian cancer as part of a weight of evidence analysis.

- **Literature Reviews, Pooled analyses, and Meta-Analyses**

A number of literature reviews, pooled analyses, and meta-analyses have been conducted over the past 30 years that have examined the association between talc use and ovarian cancer. For the purposes of this report, I have focused on the more recent studies since they evaluated a more complete set of available studies.

A 2013 pooled analysis of eight population-based case-control studies by Terry et al. (2013), investigated genital powder use and overall ovarian cancer risk by invasiveness and histologic type among 8,525 cases of ovarian, fallopian tube or peritoneal cancer and 9,859 controls. The authors concluded that genital powder use was associated with a modest increase in the risk of developing epithelial ovarian cancer (OR: 1.24; 95% CI: 1.15 – 1.33), including serous, endometrioid, and clear cell tumors. The authors reported finding "[no] significant trend ($p = 0.17$) in risk with increasing number of lifetime applications" (Terry et al., 2013). This review was limited by varying definitions of talc use (i.e., ever used, ever regularly used, used for at least six months, used for at least one year), potential recall bias, and incomplete data on genital talc use practices among the studies used for the pooled analysis.

A 2018 meta-analysis by Berge et al. analyzed 24 case-control studies (six hospital-based and 18 population-based) as well as three cohort studies, regarding the potential association between genital talc use and ovarian cancer risk. The meta-analysis identified a weak but statistically significant association between ever having used genital talc and ovarian cancer (RR: 1.22 ;95% CI: 1.13 - 1.30). The authors noted that, when examined by study design, there was an association between ever having used genital talc and ovarian cancer among the case-control studies (RR: 1.25; 95% CI: 1.17 – 1.35) but not among the cohort studies (RR: 1.02; 95%: 0.85 – 1.20). The authors stated that "the heterogeneity of results between case-control and cohort studies, however, do not support a causal interpretation of the association" (Berge et al., 2018). When reviewing tumor behavior, no difference between borderline and invasive ovarian cancer was found. When considering tumor subtype, the authors found an association between ever having used genital talc and serous carcinoma reported in 13 case-control studies (RR: 1.24; 95% CI: 1.15 – 1.34). Of the two cohort studies that reported histology-specific results, neither indicated that there was a difference between subtypes or a stronger association for serous carcinoma. The authors stated that the association between genital talc use and ovarian cancer reported in case-control studies but not in cohort studies could be attributed to bias regarding selection and retrospective self-reporting. Additionally, they noted that some recent case-control studies in which talc use was assessed after an increase in media reports regarding talcum powder litigation reported stronger associations among women who had ever used talc. The authors expressly stated that "[t]hese results may have occurred at least in part because of participants' knowledge about the latest controversies about talc use and ovarian cancer risk spread by the media," which may have contributed to recall bias (Berge et al., 2018, p. 6). Acknowledged study limitations included a lack of consistency among strategies for the adjustment for confounders and for the definition of exposure by genital talc use. The authors also stated that "[t]he biological basis and plausibility of a possible carcinogenic effect of talc on the ovaries is still not understood and remains questionable" (Berge et al., 2018, p. 8).

A 2018 meta-analysis of 24 case-control studies and three cohort studies by Penninkilampi et al. reviewed the association between perineal talc use and ovarian cancer risk. It should be noted that one of the cohorts included in the analysis was the Nurses' Health Study that was established in 1976 with data on talc use from 1982 until 1996 (Gertig et al., 2000). The authors did not include the updated information on that cohort from Gates et al. (2010). The authors found a positive association between perineal talc use and ovarian cancer, specifically of the serous and endometrioid histological subtypes. The authors stated that a positive association between ever having used talc was found among case-control studies (OR: 1.35; 95% CI: 1.27 – 1.43) but not among cohort studies (OR: 1.06; 95% CI: 0.90 – 1.25). The authors also reported an overall association between talc use and serous invasive ovarian cancer (OR: 1.25; 95% CI: 1.01 – 1.55). However as discussed, above, when including additional years of follow-up for the Nurses' Health Study, Gates et al. (2010) found a non-statistically significant association between perineal talc use and mucinous tumors but did not find any increased risk among other histologic subtypes. Another limitation of this meta-analysis was the potential for recall bias among the case-control studies used in the analysis. The authors also concluded that because the mechanism by which perineal talc use could increase the risk of ovarian cancer is uncertain, additional research was required (Penninkilampi & Eslick, 2018).

In 2019, Taher et al. conducted another meta-analysis that also considered available data regarding the potential association between perineal talc use and ovarian cancer risk. Of the 30 studies identified for review, 27 were included: three cohort studies and 24 case-control studies with a total of 16,005 ovarian cancer cases. The authors reported a "significant increase in the risk of epithelial ovarian cancer" (OR: 1.28; 95% CI: 1.20 – 1.37; P: < 0.0001; I^2: 33%) (Taher et al., 2019). However, when stratified by study type, 13 of the case-control studies showed a significant increase in risk among women who had ever used perineal talc (OR: 1.32; 95% CI: 1.24 – 1.40), while the cohort studies did not (OR: 1.06; 95% CI: 0.9 – 1.25). Of the studies that included subgroups examining the frequency and duration of use, the effect estimate for frequency of use (low to high) ranged from 1.22 (95% CI: 0.96 – 1.54) to 1.39 (95% CI: 1.22 – 1.58), respectively. The effect estimate for duration ranged from 1.22 (95% CI: 1.03 – 1.45) for less than 10 years of use to 1.19 (95% CI: 0.71 – 1.98) for 20+ years of use. The authors concluded that perineal talc use was a possible contributor to ovarian cancer risk. It should be noted that the authors drew their conclusion despite acknowledging that the certainty of the evidence was very low when applying the GRADE framework to assess the quality of the data from the studies reviewed. The initial assessment yielded a low certainty classification which was further downgraded to very low certainty when factoring in the risk of bias. The authors stated that the findings were "subject to an appreciable risk of bias, mainly due to the potential for recall bias in the included case control studies and the relatively short follow-up periods between exposure and outcome assessment in the included cohort studies" (Taher et al., 2019, p. 98).

In 2020, O'Brien et al. completed a pooled analysis of 252,044 women, 2,168 of whom were diagnosed with ovarian cancer, among four cohorts – Nurses' Health Study I and II, Sister Study, and Women's Health Initiative Observational Study – to examine the potential association between genital powder use and risk of ovarian cancer (O'Brien et al., 2020b). When examining women who reported ever-genital use of talc compared to never users, a non-statistically significant hazard ratio of 1.08 (95% CI: 0.99 – 1.17) was found. Evaluations among study

participants regarding long-term (≥20 years; HR: 1.01; 95% CI: 0.82 – 1.25) and frequent (≥1/week; HR: 1.09; 95% CI: 0.97 – 1.23) genital powder use also showed non-statistically significant hazard ratios. When examining the subgroup of women with patent reproductive systems, a hazard ratio of 1.13 (95% CI: 1.01 – 1.26) between ever users and never users was found. However, the *p* value for women with intact reproductive tracts compared to those without was 0.15, indicating that the hazard ratio did not differ significantly between these two groups. O'Brien and colleagues stated that while "there was a possible positive association among women with patent reproductive tracts … because the association was not significantly different from that observed in women with nonpatent reproductive tracts, this finding should be considered only exploratory and hypothesis generating" (O'Brien et al., 2020b, p. 56) The authors concluded that there was no statistically significant association between genital powder use and the development of ovarian cancer, and no clear dose-response trend between duration and frequency of use. However, they also noted that this study may have been underpowered to identify a small increase in risk.

O'Brien and colleagues more recently conducted a pooled retrospective analysis to assess self-reported douching and genital talc use by observing patterns of use across the life course in US women based on data collected from questionnaires, in addition to utilizing participants of the Sister Study (O'Brien et al., 2023). The criteria for eligibility included: the participant has a sister with a history of breast cancer without the actual participant having any history of breast cancer, the participant must be between the ages of 35 and 74 years of age, and the participants must be US residents, including Puerto Rico. The women were given questionnaires via a computer-assisted telephone interview and a self-administered questionnaire that discussed use of personal care products (including douche usage, application of talcum products to genitals, and haircare and cosmetic products. There was an additional follow-up questionnaire (2017-2019) that asked of the participants' individual usage of douche and talc-related products. Initally, among 36,202 women, 14% initially reported ever douching and 27% reported genital talc use. However, on the follow-up questionnaire, 51% reported ever douching, and 32% reported genital talc use. In comparison of the intial questionnaire and the follow-up questionnaire, the authors noted that 87% of particpants provided the same responses regarding genital talc use. It was specifically noted that there were indications of recall bias for genital talc use among ovarian cancer survivors.

An editorial by Gossett and del Carmen (2020) accompanied the O'Brien et al. article and stated that "the findings are overall reassuring" (Gossett & del Carmen, 2020, p. 30). The authors opined that future analyses would benefit from focusing on women with intact reproductive tracts along with details on timing and duration of exposure from perineal applications. Subsequent editorials and letters to the editor have criticized the study design and findings published by O'Brien et al., 2020 but failed to note that many of their critiques would apply to the relevant body of case-control studies as well (Cramer, 2020; Egilman et al., 2021; Gossett & del Carmen, 2020; Harlow et al., 2020). It is notable that Cramer and Egilman, each of whom authored letters to the editor criticizing O'Brien et al. (2020), have both served as plaintiffs' experts in talc litigation. Critiques raised in the various letters to the editor and editorials include the identification of incomplete or inconsistent data regarding patterns, frequency, or duration of talc use among the cohorts; that most cohort participants were postmenopausal; and that recall bias and misclassification may bias findings toward the null. In their reply,

O'Brien and colleagues stated that "because of the rarity of ovarian cancer and the risk of recall bias in retrospective studies, we think that despite the limitations, the prospective cohorts included in the analysis offered important new data for addressing this question" (O'Brien et al., 2020a, p. 2097).

In 2020, Goodman et al. conducted a weight of evidence review of the current body of literature to examine the potential association between perineal talc use and ovarian cancer (Goodman et al., 2020). Included in their review were three prospective cohorts (five publications and a pooled analysis) and 27 case-control studies (33 publications). While findings from case-control studies were varied, the authors generally observed a small increased association between perineal talc use and ovarian cancer. While the authors acknowledged that cohort studies may also be affected by bias, they noted that the potential for recall and other biases from low participation rates and the retrospective reporting of talc use may impact the case-control studies in particular with "even the higher-quality case-control studies exhibit[ing] considerable methodological limitations" (Goodman et al., 2020, p. 7). Further, the authors reported that prospective cohorts "consistently reported a null association," and there was no consistent finding of a positive exposure-response relationship among the meta-analyses (Goodman et al., 2020, p. 8). Goodman and colleagues also addressed animal studies, *in vitro* and genotoxicity data, transport studies, and exposure studies and found that overall, there were no indications of carcinogenicity, genotoxicity, transportation from the perineum to the ovaries, nor presence of particles in reproductive tissues that could be attributed to perineal talc use. The authors concluded that despite some positive associations found in case-control studies, the whole body of available evidence does not support the hypothesis that perineal talc use is associated with increased ovarian cancer risk.

Wentzensen and O'Brien (2021) completed an epidemiological review of three recent meta-analyses (Davis et al., 2021; O'Brien et al., 2020b; Terry et al., 2013) and three pooled analyses (Davis et al., 2021; O'Brien et al., 2020b; Terry et al., 2013) to assess the relationship between genital talc use and risk of ovarian cancer. The authors reported that the overall range of relative risks for ever versus never use of talc in the systematic reviews and meta-analyses included in their review was 1.22 – 1.32. When stratified by study type, in the case-control studies, the summary range of relative risks for ever versus never use was 1.24 – 1.35, while the cohort range was 1.02 – 1.08. While noting that findings from case-control studies indicated an increased risk of ovarian cancer, the authors emphasized the potential for recall bias and confounding, stating that "there are specific and well-documented concerns that differential recall bias underlies some of the associations in case-control studies of talc and ovarian cancer" and that confounding by indication cannot be ruled out (Wentzensen & O'Brien, 2021, p. 5). Further examination of the cohort studies did not reveal a statistically significant association between talcum powder use and ovarian cancer risk with the acknowledgement that the cohort studies may be limited by low ovarian cancer case numbers. The authors concluded that taken together, data from case-control and cohort studies indicate "that there may be a small, positive association between genital powder use and ovarian cancer, which may be limited to women with patent reproductive tracts" (Wentzensen & O'Brien, 2021, p. 8). They noted, however, that these associations were weak and that uncertainty regarding the underlying cause of the association warranted continued study rather than indications of a causal association. The authors concluded, "[g]iven the inability to articulate a clear causal factor to the observed associations, the lack of a good

experimental model, the lack of a specific biomarker for powder-related carcinogenesis, and the inability to rule out confounding by indication, it is difficult to conclude that the observed associations are causal" (Wentzensen & O'Brien, 2021, p. 9).

Tanha et al. (2021) completed an unmbrella review of 226 systematic reviews and meta-analyses on factors potentially associated with ovarian cancer; however, the analysis on perineal talc use was limited to four studies (Berge et al., 2018; Huncharek & Muscat, 2011; Penninkilampi & Eslick, 2018; Taher et al., 2019). A significant increased risk was found between perineal talc use and ovarian cancer (OR: 1.297, 95% CI: 1.242-1.355; RR: 1.250, 95% CI: 1.177-1.327). The authors concluded that talc use significantly increases the risk of ovarian cancer while noting that "[t]he ovarian carcinogenesis mechanism of perineal talc use has remained unclear" (Penninkilamp, 2018; Berge, 2018; Huncharek, 2011; and Taher, 2019 as cited in Tanha et al., 2021, p. 15) Although Tanha and colleagues referenced the hypothesis that talc, as an external stimulus, can ascend the female reproductive tract and promote ovarian cancer through inflammation, studies that have examined talc migration through the female reproductive tract have been inconclusive as is discussed, below.

Lynch et al. (2023) conducted a systematic review, assessing existing evidence on the potential link(s) between perineal exposure to talc-containing products (primary talcum powders and cosmetics) and female reproductive tract cancer(s). Following a comprehensive literature search, data abstraction and quality evaluation, the authors critically evaluated 40 primary studies (36 human studies and 4 animal studies) that discussed talc exposure and female cancer risks in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) checklist. All studies were classified based on strength of evidence. According to the authors, the methodology used mirrored that which they published in Lynch et al. (2022). The authors found indeterminate evidence of carcinogenicity in animals associated with talc exposure. According to the authors, the weight-of-evidence suggests no associations between talc exposure and carcinogenesis. Overall, the authors indicated "evidence of no association between perineal application of talcum and ovarian cancer" at human-relevant exposure levels, "evidence of no association for endometrial cancer[,] and insufficient evidence to determine whether a causal association exists between genital talc application and cervical cancer.

In a recent systematic literature review, Woolen and colleagues examined the association between frequent perineal exposure to talc and ovarian cancer and followed their review with a meta-analysis. The study protocol was based on the International Prospective Register of Systematic Reviews, and the meta-analysis on the Meta-analyses of Observational studies (MOOSE) guidelines. Searches were conducted in the databases PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials. Observational cohort and case-control studies were included if they studied risk of ovarian malignancy and contained primary data on frequent (twice or more per week) applications of perineal talc with direct application to the perineum and rectum, underwear or sanitary napkins, and/or on birth control devices like diaphragms. Other talcum powder application was excluded, leaving 11 studies for analysis with a total of 6,542 ovarian cancer cases and 66,876 total women. Talcum powder use ranged from four to seven times per week, and 45% of women reported daily exposure. The authors specifically note that when duplicate reports of the same subjects were published, the

publication reporting the highest talc use was selected. Despite differences in study design, the included studies were relatively homogenous in their effects (I2=18.1%, p=0.272). The pooled adjusted odds ratio between the frequent use of perineal talcum powder products and ovarian cancer was 1.47 (95% CI: 1.31-1.65), an effect that was consistent in direction among cohort and case-control studies. However, several studies with frequent use may have been excluded due to insufficient questionnaire detail, which resulted in a potential source of bias for pooled estimates. Use definitions differed across studies, which makes the interpretation of pooled estimates slightly more difficult (Woolen et al., 2022). Additionally, the authors note that O'brien (2020) only found significant results when their analysis was restricted to women with patent fallopian tubes, and therefore only included that analysis within their literature review. Finally, it is noteworthy a co-author of this study, Rebecca Smith-Bindman, MD, served as a paid expert witness for plaintifs in talcum powder litigation of this publication.

10.1.5 Additional Studies in Humans Relevant to Ovarian Cancer

- **Studies on Talc Migration in the Female Reproductive System**

Several histological studies in humans have reported on the presence of talc in ovarian tumors and tissues. The first identified talc particles in 10 of 13 ovarian tumor tissues examined, as well as 5 of 12 normal ovarian tissues. No information regarding talc exposure among the patients was reported. The authors noted the "preliminary" nature of their observations and stated that "it is impossible to incriminate talc as a primary cause of carcinomatous changes" (Henderson et al., 1971, p. 271). A subsequent editorial response noted that the original study "merely drew attention to the presence of talc in the tissue and did not suggest that it was the cause of malignancy" (Henderson et al., 1979, p. 499). The editorial also recognized that talc present on surgeons' gloves may have been a source of contamination and that talc burden was similar across normal and cystic ovarian tissues and adenocarcinoma.

Heller et al. (1996) examined ovarian tissue from women with the intent to correlate talc burden with history of perineal talc use. Talc particles were detected via polarized light and electron microscopy in all examined tissue regardless of reported perineal talc use. The authors stated that because "[t]alc particle counts were completely unrelated to reported levels of perineal talc exposure," their "results do not support a dose-related ovarian talc particle burden" (Heller et al., 1996, pp. 1507, 1509). A subsequent study concluded that although talc particles have been found in human ovarian tissue and particle migration is plausible, the particle burden does not support the hypothesis that this migration is related to the causation of ovarian cancer (Whysner & Mohan, 2000).

Cramer et al. (2007) examined the pelvic lymph nodes of one ovarian cancer patient who was reportedly a long-term talc user – having applied talc to her perineum, underwear, and sanitary napkins daily for 30 years – and found birefringent particles "compatible with talc" when using PLM, SEM, and EDX (Cramer et al., 2007, p. 499). The authors opined that talc need not reach the ovaries to affect ovarian cancer risk, citing the potential for

inflammation in the lower genital tract. At the time of publication, the authors reported having started "a more extensive study" examining the relationship between particles in pelvic lymph nodes and ovarian cancer.

In 2019, McDonald et al. conducted two studies to examine the pelvic organ tissue (McDonald et al., 2019a) and lymph nodes (McDonald et al., 2019b) of women with ovarian cancer and a history of talc use. In their pelvic organ tissue study, the authors included five ovarian cancer patients with a history of perineal talc use and six ovarian cancer patients with no history of talc use. Birefringent particles were found in various pelvic region sites, including the ovaries, in all five of the talc-exposed patients when examined by PLM. Talc particles were also reportedly found in the ovaries of all five talc-exposed patients when examined by SEM/EDX. Among the cases with no history of talc exposure, birefringent particles were found in the ovaries of five of the six women, and talc particles were found in the tissue of two of the women, each of whom had a history of pelvic surgery. McDonald and colleagues emphasized the importance of lymphatics as a likely pathway for talc migration. In their lymph node study, the authors included 22 ovarian cancer patients, 10 of whom had a history of perineal talc use, to differentiate between talc related to personal exposure and talc from laboratory contamination. The authors reported that, after adjusting for surface contamination, the talc burden found in lymph nodes correlated strongly with perineal talc use using digestion and SEM/EDX examination. A second group of lymph nodes from 10 ovarian cancer cases was also studied to examine the relationship between birefringent particles found in lymph node parenchyma and talc particles found deeper within those tissue blocks by SEM/EDX. Of note, no information regarding talc exposure was available. Birefringent particles were found in all 10 cases, while talc particles were found in eight cases. From their lymph node study, McDonald and colleagues concluded that talc surface contamination is common and that perineal talc exposure frequently "results in significant deposition of talc in the tissues" (McDonald et al., 2019b, p. 14). Notably, SEM/EDX was not performed on the group of 22 cases. The authors attempted to address this shortcoming by associating the two patient groups, stating that, "by showing that birefringent particles within lymph nodes were strongly correlated with the demonstration of talc inside the nodes by *in situ* SEM/EDX, the second part of our study filled that role" (McDonald et al., 2019b, p. 13).

In summary, studies investigating ovarian tissue for the presence of talc particles among talcum powder users are inconclusive. The available studies have not shown a dose-response relationship between tissue talc burden and reported perineal talc use. Additionally, talc has been identified in tissue obtained from women who did not report perineal talc use, as well as those who did report such use. Thus, based on the scientific literature, it is apparent that perineal talc use is not directly associated with any potential talc tissue burden in the female reproductive system.

- **Studies on Inflammation and Ovarian Cancer**

It has been hypothesized that talc may contribute to or cause the development of ovarian cancer by way of inflammation. I have considered studies that examined this hypothesis, as well as studies regarding the potential for reduced risk of ovarian cancer through the use of anti-inflammatory drugs.

In their 2019 analysis of 13 studies that included 758,829 women who reported analgesic use, 3,514 of whom developed ovarian cancer, Trabert et al. found varying results among women who used aspirin, non-aspirin NSAIDs, and acetaminophen (Trabert et al., 2019). The authors reported that women who used aspirin at least six days per week for less than ten years had a reduced risk of ovarian cancer. However, frequent (four days per week) aspirin use, non-aspirin NSAID use, and acetaminophen use were not associated with increased risk. Conversely, daily acetaminophen use and frequent, long-term use (at least ten years) of aspirin and non-aspirin NSAIDs were associated with an increased risk of ovarian cancer. In the most recent PDQ issued in July 2021, NCI included anti-inflammatory drugs in the list of factors with inadequate evidence of an association with ovarian cancer risk (NCI, 2023). Included in the NCI review was reference to a meta-analysis of 21 observational studies, that reported a decreased risk of invasive ovarian cancer among aspirin users but no statistically significant association with non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), prompting the authors to conclude that "[f]urther research on NSAIDs and ovarian cancer is needed before definite conclusions can be drawn" (Baandrup et al., 2013).

Studies that have examined a history of pelvic inflammatory disease (PID) and ovarian cancer risk have resulted in mixed findings. In their 2008 case-control study of 1,576 women with ovarian cancer and 1,509 controls, Merritt et al. found that regular use of aspirin and NSAIDs was only associated with a decreased risk of low malignant potential ovarian tumors and concluded that chronic inflammation is not associated with the development of ovarian cancer (Merritt et al., 2008). In a 2014 cohort of 888 women with a history of pelvic inflammation and 552 without, a significant increased risk of ovarian cancer was not found among women with a history of pelvic inflammation (McAlpine et al., 2014). However, the authors concluded that pelvic inflammation may be a contributing factor to the development of ovarian cancer due to a statistically significant increased risk of ovarian cancer when comparing the study population to the general population using the British Columbia Cancer Agency database. Shen et al. (2016) found no increased risk of ovarian cancer in 32,268 patients when comparing equal numbers of those with and without PID.

In 2018 and 2020, Stewart et al. reviewed the association between PID and various histotypes of ovarian cancer (Stewart et al., 2018, 2020). In their cohort of 441,382 Australian women, 454 of whom were diagnosed with high-grade serious ovarian carcinoma (HGSC), the authors found that a history of PID was associated with an increased risk of HGSC (Stewart et al., 2018). In a study involving the same cohort of 441,382 women in 2020, the authors found that a history of PID was associated with an increased risk of serous borderline tumor (SBT) and low-grade serous carcinoma (LGSC) (Stewart et al., 2020). No association was found between PID and mucinous borderline tumors (MBT).

Rasmussen et al. (2016) also found an increased risk of SBT among women with a history of PID when studying 1,318,925 Danish women, 81,263 of whom were diagnosed with PID and 2,736 diagnosed with borderline ovarian tumor. No association was found when examining MBT and it was noted that the current body of literature on the association of PID and borderline ovarian tumors is limited and that additional studies are needed (Rasmussen et al., 2016). A subsequent review of 1,318,929 Danish women (81,281 with PID and 5,356

with ovarian cancer) found that PID was modestly associated with an increased risk of serous ovarian cancer only and not with ovarian cancer overall. The authors concluded that "[a]lthough the increased risk of serous ovarian cancer associated with PID was statistically significant, the association was modest in strength, indicating that PID is not a strong risk factor for ovarian cancer" (Rasmussen et al., 2017a, p. 108). In the same year, Rasmussen et al. also conducted a pooled analysis of 13 case-control studies to investigate the association between PID and risk of ovarian cancer among 9,162 women with invasive ovarian cancer, 2,354 women with borderline tumors, and 12,736 controls (Rasmussen et al., 2017b). They found an increased risk among women with borderline tumors but not with overall ovarian cancer risk.

Based on the hypothesis that early stages of ovarian cancer can be found in the fallopian tube, Malmberg et al. (2016) conducted a case-control study of 60 women in the "hereditary group" (who underwent risk-reducing removal of the ovaries and fallopian tubes), 18 women in the "sporadic serous cancer group" (who underwent surgical resection of ovarian cancer without a known hereditary component), and 23 controls to examine the incidence of serous tubal intraepithelial carcinoma (STIC) and whether chronic fallopian tube injury can lead to the development of cancer (Malmberg et al., 2016). An elevated, but not statistically significant, association was found in the sporadic serous cancer group. The authors concluded that "no significant correlation was made between serous carcinoma and histological signs of inflammation or chronic tubal injury" (Malmberg et al., 2016, p. 712). In 2018, Visvanathan et al. also studied the relationship between fallopian tube lesions and ovarian cancer risk and found no statistically significant association between ever having used talc and developing STIC and/or invasive carcinoma (Visvanathan et al., 2018).

A 2017 meta-analysis of six cohort and seven case-control studies found that PID was associated with an increased risk of ovarian cancer, particularly among Asian women (Zhou et al., 2017). The authors also reported that this association "seemed to be most apparent in analyses of borderline ovarian tumors" (Zhou et al., 2017, p. 427)

Most recently, Piao et al.'s (2020) meta-analysis of seven cohort and nine case-control studies found an association between PID and ovarian cancer overall that was most consistent among Asian women and in case-control studies when subgroup analyses were performed (Piao et al., 2020). Piao and colleagues also reported that "PID is a diffuse group of inflammatory conditions, which may have differing roles in the pathologies of ovarian cancer and differing ovarian tumor risks" and that "most studies did not indicate the cause of PID or report information about PID exposure" (Piao et al., 2020, p. 546) In summary, the authors noted that large, well-designed studies that accurately assess PID and ovarian cancer are needed to confirm the results found.

In summary, while some studies have reported an association between PID and some types of ovarian cancer, it is clear that the association (if any) is weak and inconsistent, which does not support the notion that general chronic inflammation can cause ovarian cancer. This, coupled with the fact that studies examining anti-inflammatory medications failed to show consistent reduction in ovarian cancer, undermines the theory that ovarian cancer is a product of talc-induced inflammation.

10.1.6 Animal Toxicology Studies

- **Carcinogenic Evaluation**

Numerous animal studies have examined cancer incidence in response to cosmetic talc exposures via various routes of administration. Inhalation studies conducted with talc were designed to produce a consistent airborne concentration throughout the test chamber. This contrasts with experimental designs with nose-only exposure, or exposure only in the breathing zone of the animals. Whole-body exposures resulting from the presence of talc throughout the test chamber are particularly relevant in this matter as test particles settle on all available surfaces, including the animal's body surface and the perineal region. As noted by Boorman and Seely in the study on the ovarian effects of lifetime exposure to talc in mice and rats, the test conditions resulted in "talc covering the fur and cage bars, [and] there was ample opportunity for perineal as well as oral and respiratory exposure" (Boorman & Seely, 1995, p. 242).

Wehner et al. (1977b) exposed hamsters to aerosolized Johnson's Baby Powder under two regimens: 9.8 mg/m^3 for 3, 30, or 150 minutes per day, five days per week for 30 days, or 8.1 mg/m^3 for 30 to 150 minutes per day, five days per week, for 300 days. Histopathological examination of numerous organ systems, including the ovary, revealed no treatment-related tumors.

In 1993, the National Toxicology Program (NTP) conducted a two-year carcinogenicity study of talc in rats and mice (NTP, 1993). The test material used in this study was described as a non-asbestiform, cosmetic grade, micronized talc product with a maximum particle size of 10 µm. Animals were exposed to target concentrations of 6 and 18 mg/m^3 for six hours per day, five days per week for approximately two years. In an extension of the study, Boorman and Seely (1995) reported no increases in ovarian lesions among talc-treated female rats and mice compared to controls.

The NTP study reported an increase in lung and adrenal gland tumors among rats, but not mice. The study concluded that that there was "some evidence of carcinogenic activity" for talc in male rats based on an increased incidence of pheochromocytomas of the adrenal gland and "clear evidence of carcinogenic activity" for talc in female rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and pheochromocytomas of the adrenal gland. One malignant mesothelioma was observed in a male rat in the highest exposure group. Numerous authors have criticized the NTP study based on a number of methodological flaws, including the use of micronized talc not reflective of particle size used in consumer products, excessive aerosol concentrations leading to lung burden overload, sex-specific results, and inconsistent exposure concentrations (Addison & Langer, 2000; Carr, 1995; Fiume et al., 2015; Musser, 2014; Wehner, 1994, 2002). Lung overload is a condition often seen in experimental studies in rats when excessive airborne concentrations of test particles overwhelm clearance capacities of the lung. This can lead to secondary stress and tumor formation secondary to any direct effects of the test article. Other particulates such as titanium dioxide, carbon black, coal, and diesel soot have produced pulmonary effects including adenoma/carcinoma induction in rats under conditions of particle overload (ILSI, 2000; Oberdorster, 1995). An expert panel convened

in 1994 stated that the NTP study "has no relevance to human risk" in part due to issues related to lung overload (Musser, 2014, p. 4).

Other researchers have specifically evaluated the effects of talc on ovarian tissue following intrabursal, intravaginal and perineal routes of exposure. Hamilton et al. (1984) administered a single dose of Italian grade talc to female rats via intrabursal injection. Changes in ovarian and surrounding tissue were followed over the course of 18 months with no reported neoplasms. Papillary changes in the surface epithelium of the ovaries were observed in four of 50 talc-treated animals, while foreign body granulomas were reported in five animals. The authors stated that while "[i]t is clearly tempting to attribute the papillary change in the surface epithelium of injected ovaries to the direct effects of exposure to talc," the observed changes may be due to long term exposure to a "high concentration of steroid hormones present in the entrapped follicular fluid within the distended bursa" (Hamilton et al., 1984, p. 105).

More recently, Keskin et al. (2009) evaluated histopathological changes of the peritoneum and female reproductive system following sub-chronic exposure to talc. Female rats received intravaginal or perineal application of 100 mg talc in saline on a daily basis for three months. While the authors reported finding foreign body reaction, infection, and an increase in inflammatory cells in treated animals, there was no evidence of neoplastic changes.

Several other animal studies have evaluated carcinogenic potential of talc following administration via intraperitoneal or intrapleural injection or intratracheal instillation, none of which reported an increased cancer incidence following talc exposure (Jagatic et al., 1967; Ozesmi et al., 1985; Pott et al., 1974).

In summary, no animal study has identified an association of cosmetic talc exposure with cancer development, including ovarian cancer. This is consistent with the conclusion reached by IARC that animal studies provided "limited evidence" for the carcinogenicity of talc not containing asbestos or asbestiform fibers (IARC, 2010).

- **Deposition of Talc in Ovaries**

In addition to the human studies described above, several animal studies have examined the ability of talc to translocate or migrate from the site of exposure, including inhalation and perineal routes, to ovarian tissue. Wehner et al. (1977a) exposed hamsters to "neutron-activated" Johnson's Baby Powder via inhalation. Animals were exposed to a total of 360 to 570 µg of talc over the course of two hours and followed for a period of 132 days. While a small increase in talc was identified in the ovaries of treated animals via gamma-ray analysis, this finding was not significant compared to control animals. The authors concluded that there was no evidence that talc translocated to the ovaries or other organs, including the liver and kidney, following inhalation exposure (Wehner et al., 1977a). Boorman and Seely (1995) noted in an extension of the NTP (1993) study, that there was no talc found in the ovaries of rats and mice exposed via inhalation for a period of two years.

Henderson et al. (1971, 1979) reported that talc particles were present in the ovaries of rats following intrauterine and intravaginal exposures to talc. It should be noted that the results presented in this study were

extremely limited and did not provide any indication of how much talc was identified in ovarian tissue of the treated animals. In contrast, other researchers have similarly administered talc via intravaginal and perineal routes and failed to find talc in ovarian tissue following single or repeated doses (Phillips et al., 1978; Wehner et al., 1985, 1986). Specifically, Wehner et al. (1985) applied a single dose of a slurry containing "neutron-activated" talc into the vagina of monkeys. The authors reported no measurable translocation of talc particles to areas outside of the application site up to 72 hours post-administration. Wehner and Weller (1986) administered 30 doses of 125 mg of "neutron-activated" cosmetic talcum powder intravaginally to monkeys over a 45-day period. Gamma-ray analysis found evidence of activated talc in the vagina and cervix of treated animals, while no measurable levels were observed in the ovaries, oviduct, nor uterus.

Together, these studies demonstrate that there is limited evidence that talc can translocate through the body from the site of exposure, whether occurring via inhalation or perineal exposure, to the ovaries in animals. The majority of studies that did identify talc particles in the ovary were based upon direct administration into the female reproductive tract via intrauterine or intravaginal applications and did not consider perineal exposures. In its evaluation of similar studies, IARC stated that animal studies "showed no evidence of retrograde transport of talc to the ovaries" (IARC, 2010, p. 411). Thus, there is no evidence from experimental animal studies that talc applied to the perineum is capable of migrating through the female reproductive tract to the ovaries.

10.1.7 Cellular/Mechanistic Studies of Talc Toxicology

Mechanistic studies, which can be conducted in animals and in human/animal tissues or cells (*in vitro*), are primarily conducted with an aim to understand the biological relevance, if any, of underlying mechanisms that may lead to the observed toxicological effect in animals and/or humans. One advantage of animal and cellular studies is their ability to be well-controlled in a laboratory to reduce influence of confounding factors. While information from mechanistic studies can be informative and help in designing additional follow-up studies, these studies alone cannot establish causation between chemical exposure and disease. Additionally, many of these types of studies reported in the scientific literature may utilize varied and non-guideline assay methods, may require non-relevant routes of administration, and/or use cytotoxic chemical concentrations which can confound assay results. In particular, *in vitro* studies are intended for screening, predicting or discovery purposes with the understanding that utility to directly inform human health risk may be limited (OECD, 2018). USEPA carcinogenic risk assessment guidelines state that "a higher level of confidence is generally given to data that are derived from *in vivo* systems, particularly those results that show a site concordance with the tumor data" (USEPA, 2005, pp. 2–36). As such, the results of animal studies that measure the actual toxicological effect following exposure to a chemical generally supersede the results of *in vitro* assays (USEPA, 2005).

While properly conducted mechanistic studies may be useful to inform the direction of further follow-up studies, they must be considered within the context of the entire body of evidence to draw conclusions about the relevance to human health risks. They cannot, by themselves, establish causation between chemical exposure and disease outcomes (OECD, 2019). USEPA cancer guidelines "emphasize the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents" (USEPA, 2005, pp. 1–11).

The Organization for Economic Co-operation and Development (OECD) also outlines several key criteria that must be evaluated to determine the appropriateness and reliability of mechanistic studies for supporting human health risk (OECD, 2019). These criteria include ensuring that: important factors such as basic quality control and quality assurance standards are met; studies follow generally accepted protocols with preference toward validated guideline methods; the chemical is administered by a relevant route of exposure and in relevant non-cytotoxic concentrations; and the proposed mechanism of action is relevant to biological pathways in humans. I have provided a summary of recent studies addressing potential carcinogenic mechanisms of action for talc along with considerations for relevance to humans.

Various studies have evaluated the genotoxic potential of talc under both *in vivo* and *in vitro* experimental systems. A battery of assays that examined DNA damage and repair, chromosomal changes, and mutagenicity demonstrated that talc is not genotoxic (Dreher et al., 1978; Endo-Capron et al., 1990, 1993; USFDA, 1974; Van Wissen & Prop, 1972). This is consistent with the current scientific consensus that talc does not exhibit genotoxic activity (Fiume et al., 2015; Goodman et al., 2020; USEPA, 1992). Regarding genotoxicity, IARC stated that "no data were available on the genotoxic effects of exposure to talc in humans. The limited number of studies available on the genetic toxicology of talc *in vitro* gave negative results" (IARC, 2010, p. 411). More recently, Goodman et al. (2020) concluded that "[t]here is little information regarding the potential for talc to initiate changes in DNA …, the limited information that is available is mostly negative and does not indicate that talc is genotoxic (p. 22).

Others have looked specifically at potential mechanisms of action including inflammation, oxidative stress, gene expression changes, and cellular transformation in ovarian cells treated with talc preparations.

Buz'Zard and Lau (2007) examined talc-induced carcinogenesis in "immortalized normal" human ovarian epithelial (OSE2) and stromal (GC1a) cell lines (p. 580). The authors reported an increase in cell viability with talc up to 100 µg/ml in both ovarian cell lines, and a statistically significant increase in reactive oxygen species (ROS) production in epithelial (20 µg/mL at 72 and 120 hours; 50 µg/mL at 120 hours) and stromal cells (0.5 µg/mL, 20 µg/mL, and 50 µg/mL at 72 and 120 hours; 5 µg/mL and 100 µg/mL at 120 hours) was observed following an initial reduction. Neoplastic transformation was evaluated as the ability of talc-treated cells to grow suspended in soft agar. An increase in the number of transformed colonies was observed with talc-treatment (5 µg/mL and 20 µg/mL in epithelial cells; 5 µg/mL, 20 µg/mL, and 100 µg/mL in stromal cells) following 14-day incubation in soft agar. The authors concluded that "talc may contribute to ovarian carcinogenesis in humans by way of inducing aberrant ROS generation" (Buz'Zard & Lau, 2007, p. 586). The study had several limitations in addition to the use of immortalized cells. First, the authors do not address the lack of dose-dependent response in many of the endpoints examined. For example, ROS production and cell growth/transformation were significantly decreased at the higher talc concentrations. In addition, the authors demonstrated significant changes in cell viability following talc treatment. However, there is no indication that the ROS production data was normalized to cell viability or number. By comparing values (e.g., percent fluorescence) from talc-treated cells with untreated control cells without accounting for cell viability and/or proliferation, it is likely that changes may be

skewed by the number of cells present at the time of the assay. In addition, induction of ROS and oxidative stress is a non-specific response also seen with non-carcinogenic substances (Smith et al., 2020). Therefore, ROS production or oxidative stress markers alone are not sufficient to imply carcinogenicity without further evidence such as accompanying genotoxicity, which is lacking for talc. As noted previously, immortalized cells are advantageous in the laboratory for their ability to continuously proliferate. Other researchers have demonstrated the ability of "normal" immortalized cell lines to grow in soft agar as a result of cellular changes and transformation resulting from continuous growth in culture alone and not attributed to a known or suspected carcinogen (Jin et al., 2006; Schwab et al., 2000).

Shukla et al. (2009) and Hillegass et al. (2010) compared gene expression changes in human ovarian epithelial cells treated with non-fibrous talc and crocidolite asbestos. In the first study, the authors reported that non-fibrous talc did not exhibit cytotoxicity, and no significant changes in gene expression were observed in ovarian epithelial cells. In contrast, high levels of crocidolite asbestos (75 $\mu m^2/cm^2$) resulted in changes in the expression of two genes, while lower concentrations (15 $\mu m^2/cm^2$) did not (Shukla et al., 2009) Similarly, Hillegass et al. (2010) reported that microarray data indicated a reduced response for non-fibrous talc compared to crocidolite asbestos in ovarian epithelial cells. Each of these studies presented limited data regarding ovarian epithelial cells, yet noted a muted response, if any, upon treatment compared to mesothelial cells. The authors stated that these results were "not surprising since the [ovarian epithelium cell type] is not implicated in asbestos-induced diseases and was included essentially as a control" (Hillegass et al., 2010, p. 429).

Mandarino et al. (2020) (co-authored by a frequent plaintiffs' expert in talc litigation), and a follow-up study by Emi et al. (Emi et al., 2021) examined the effect of talc, with or without estrogen present, on phagocytic cells, including gene expression and the ability to modulate ovarian cancer cell growth and survival. In the initial study by Mandarino et al. (2020), the authors reported that phagocytic cell lines treated with talc exhibited (1) a significant increase in ROS production with an additive effect in the presence of estrogen; and (2) gene expression changes compatible with cell proliferation, tumor environment promotion, and decreased immune surveillance in two of three cell lines. Further, a non-significant increase in survival of ovarian cancer cells was observed when co-cultured with talc-treated phagocytic cells as compared to non-talc-treated control cells. In the subsequent study by Emi et al. (2021), gene expression changes related to cell proliferation, immune and inflammation response, and epigenetic changes were seen in talc-treated phagocytic cells to a greater degree than observed with titanium dioxide particles. The authors suggested that these results support altered macrophage function in terms of anti-tumor activity following talc treatment in the presence of estrogen, while noting that further research on the issue is required. Notably, *in vivo* studies have examined phagocytic cell function in rodents following talc exposure (Beck et al., 1987; NTP, 1993). Beck et al. (1987) found a persistent decrease in macrophage phagocytosis activity up to 14 days post-intratracheal instillation in hamsters. A similar exposure concentration-dependent decrease was observed in alveolar macrophages from mice, but not rats following inhalation exposure (NTP, 1993). Thus results of these studies were varied and the likelihood of lung overload contributing to any decreases in alveolar macrophages in experimental animals cannot be excluded. Importantly, an opposing association was seen between species-specific changes in alveolar macrophage

number and tumor incidence, in that lung adenomas and carcinomas were only observed in rats which did not present changes in alveolar macrophages with talc-treatment (NTP, 1993).

In summary, the limited data from *in vitro* and animal studies provide inconclusive data regarding the impact of phagocytic cell changes and subsequent carcinogenesis related to talc.

Dr. Ghassan Saed, who has been retained as a plaintiff's expert in this litigation, has conducted recent *in vitro* research along with several colleagues, purporting to show that talc induces oxidative stress, inflammation, cell proliferation, among other "hallmarks of ovarian cancer" and "malignant transformation" (Fletcher et al., 2019, p. 5; Harper et al., 2020). Fletcher et al. (2019) evaluated potential associations between talcum powder exposure and gene expression changes in ovarian cancer and non-cancer cell lines. The authors indicated that ovarian cancer cells and normal ovarian cells treated with Johnson's Baby Powder dissolved in DMSO showed increased cell proliferation, significant increases in select prooxidant genes (e.g., iNOS, myeloperoxidase), decreases in antioxidant gene expression (e.g., catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase), and increased inflammation in the form of the tumor marker CA-125. Based on these results, the authors concluded that the cellular effects of talc supported an association between genital use of talcum powder and increased risk of ovarian cancer development. Further, they stated that the study results "have shown beyond doubt that talc alters key redox and inflammatory markers, enhances cell proliferation, and inhibits apoptosis, which are hallmarks of ovarian cancer" (Fletcher et al., 2019, p. 5). In a follow-up study[1], Dr. Saed and colleagues examined levels of cell proliferation and apoptosis through immunohistochemical (IHC) staining of Ki-67 and p53 proteins associated with these processes in cultured ovarian cells exposed to Johnson's Baby Powder suspended in phosphate-buffered salin (Harper et al., 2023). The authors reported a dose-dependent increase in transformed ovarian cells following treatment with 100 µg/ml and 500 µg/ml talcum powder in addition to increased immunostaining for Ki-67 and mutant p53, diagnostic markers of ovarian cancer subtypes. Talc-treated primary human peritoneal fibroblasts, nor ovarian cells treated with titanium dioxide exhibited, similar effects. The authors concluded that the results "clearly demonstrate … malignant transformation" of the cultured cells following talcum powder exposure (Harper et al., 2023, p. 156).

- **Critical Analysis of Studies from Dr. Saed and Colleagues**

The work of Dr. Saed and colleagues warrant additional discussion due to the significant methodological flaws and overstated conclusions that appear in the authors' work. One of the major limitations of the described studies is the lack of characterization of the talc article used in the experiments. In particular, Fletcher et al. (2019) described that the talcum powder was "dissolved in dimethyl sulfoxide [DMSO] … and was filtered with a 0.2 µm syringe" (p. 2). The procedure and dissolving and filtering talcum powder must be called into question. Notably, in the subsequent work of Harper et al. (2023), the authors changed their method of preparing the test

[1] Based on documents provided in this case, it is my understanding that the manuscript describing these studies was submitted for publication to no less than four scientific journals that rejected its publication. The manuscript was accepted for publication in November 2021. I have reviewed various versions of the manuscript submitted for publication which in part form the basis of my opinions expressed in this report.

articles, where talcum powder was now suspended in PBS (instead of DMSO), sonicated and filtered using a 30 µm filter (150 times larger in size than in the previous study). As such, the different preparation techniques likely resulted in test articles with drastically different compositions between the two studies. Regardless of the preparation techniques, a minimum set of characterization information for the test article in question is necessary in order to interpret results from toxicity testing. This is particularly true with particle toxicology in which a wide range of physicochemical properties mediate the interaction of substances with cells, tissues, and organ systems. These properties include chemical composition, size, dimension, surface area, agglomeration state, surface chemistry, biopersistence, and bioavailability of particles (Klaassen, 2013, pp. 1192–1197). The use of dissolved and filtered talcum powder as performed by Fletcher et al. (2019) likely disrupts many of these potential mediators of toxicity and/or eliminates a particular size of talc particles by filtering out certain particle sizes from the suspension. However, the overall effect of such techniques on particle size distribution or agglomeration are unknown since the authors did not perform any characterization of the talc or control (titanium dioxide) articles aside from non-specific visual examination. In addition, it is unclear if DMSO had any potential interferences in the experimental assays, particularly since DMSO may have significant effects on cellular functions, even at low concentrations (0.1%) (Verheijen et al., 2019).

Dr. Saed and colleagues chose doses for their experiments (e.g., 100 and 500 µg/ml) that were not based on any relevance to actual human exposures or internal doses. As stated in the subsequent papers, doses were based on "previous studies which showed talcum powder to induce changes in redox balance of cells at the molecular level" (Harper et al., 2023, p. 152). The authors cited the study of Fletcher et al. (2019), which based upon the test article preparation (e.g. dissolved in DMSO, filtered using 0.2 µm syringe) is likely a distinct test article than that of the Harper et al. (2023) study, for reasons that I have described in the preceeding paragraph. Therefore, the results from these two studies are not comparable. The issue of dose relevance in Dr. Saed's recent paper was highlighted by many reviewers, as discussed below, as well as one of the study authors (Robert Morris), who asked Dr. Saed and colleagues prior to manuscript submission, "[a]re the concentrations used physiologically possible (especially in the ovary)?" (Communication from Robert Morris 7/20/2020). Dr. Saed and colleagues stated in the manuscript that "[t]hese doses are not intended to represent a typical dose when applied to the genital area in women over time," and further identified the experimental dosing regime as a limitation but failed to appreciate or acknowledge that this methodological flaw restrains the interpretation of results or translation to animals or humans (Harper et al., 2023, p. 155).

Further, the experiments conducted by Dr. Saed and colleagues are not sufficient to allow for broad statements regarding carcinogenic potential. Donaldson et al. (2009) cautioned against interpretations on particle toxicology solely based on *in vitro* approaches, noting that similarities in oxidative stress and inflammatory responses do not translate to particle-specific pulmonary and extra-pulmonary health effects, including cancer development, observed in experimental animals and humans. In addition, it is not known whether the increased expression of

p53, as reported in the submitted manuscript version[2], which could be a temporary response to stress, indicates or could lead to actual mutations. p53 is involved in a variety of cellular responses including cell-cycle control, cellular stress responses, DNA repair, and apoptosis (Rufini et al., 2013). Although the p53 tumor suppressor gene (*TP53* in humans or *Trp53* in mice) is mutated in nearly all high-grade serous ovarian cancer (HGSOC) cases, experiments with mouse models indicate that a p53 mutation alone does not cause ovarian tumors; rather, multiple mutations are required, which is in alignment with the current understanding of multi-hit cancer development, or a combination of genes that must be mutated for cancer development to be possible (Yamulla et al., 2020). For example, simultaneous inactivation of *Trp53* and *Brca1* (often mutated in HGSOC), was incapable of causing transformation in mice (Xing & Orsulic, 2006). However, activation of Myc (a gene that, when mutated, can cause normal cells to become carcinogenic) in addition to combined *Trp53* and *Brca1* disruption successfully initiated HGSOC. Yamulla et al. recently reported that *TP53*, *PTEN*, and *RB1* are a core set of alterations required for ovarian cell transformation (Yamulla et al., 2020). Thus, the immunohistochemistry results described in Dr. Saed's manuscript would be considered incomplete and do not support the interpretation by the authors that functional changes can take place in the cell following exposure to talc, or that this limited information can predict the ability of talc (or any material) to elicit carcinogenesis *in vivo*. Finally, cell transformation assays have been identified as critical tests to predict carcinogenic potential for various substances, although there are concerns regarding the applicability and performance of such assays (Creton et al., 2012). One study conducted by OECD found that the rate of false positives across assays in multiple cell types was as high as 47% (Vasseur & Lasne, 2012).

These and other flaws were highlighted in scathing peer-review comments from reviewers for several journals that rejected the manuscript. The reviewers took particular issue with the lack of relevance of the experiments to human perineal exposures and expressed concern that the doses were chosen without sound reasoning and that they would not represent actual exposure conditions (cited quotes provided below). Additionally, all three rejection responses from the journals included comments regarding the lack of material characterization. Reviewers also commented that the authors cannot claim malignant cell transformation occurred based on the results of a cell transformation assay (SAED_SEPT222021_SUPPL_000069), and alternate explanations for the reported results were provided, including that the cell seeding density (which was calculated by one reviewer to be approximately 90 times too high) could have caused a stress response itself, which is "not an indication of cell transformation associated with tumorigenesis" (SAED_SEPT222021_SUPPL_000102).

Reviewers also commented that the manuscript was not technically sound, the data had not been subjected to a proper statistical analysis, and the data were not presented in a way that was "clear, correct, and

[2] Dr. Saed and colleagues interpreted their results as evidence of mutations, but they apparently did not perform any sequencing analysis and therefore appear to infer mutation from differing expression patterns. As one peer reviewer noted, "p53 expression at a single time point following treatment cannot differentiate between novel mutations and physiologic responses to a given treatment condition" (SAED_SEPT222021_SUPPL_00070). Moreover, Dr. Saed's laboratory notebook appears to contradict the finding as reported in the submitted manuscript version, at least as to one cell line. Specifically, the laboratory notebook reports that the HOSPIC control displayed mutated p53 whereas the talc-treated HOSPIC cells displayed wild-type p53 (SAED_SEPT222021_SUPPL_000171).

unambiguous" (SAED_SEPT222021_SUPPL_000100, SAED_SEPT222021_SUPPL_000101). Moreover, reviewers pointed out that there are both careless errors throughout the manuscript, including grammatical issues and misrepresentation of cited papers, as well as large sections of text that are copied from websites (SAED_SEPT222021_SUPPL_000070). Importantly, though a team was involved with the overall production of this manuscript, Dr. Saed's listed roles in the cover letter in his submission to Gynecologic Oncology reveals that it was he alone who was responsible for writing the manuscript. In contrast, the recently accepted version noted that other authors helped in writing the manuscript (SAED_SEPT222021_SUPPL_000071; Harper et al., 2021).

The fact that multiple journal editors did not offer Dr. Saed and colleagues an opportunity for resubmission following revision further highlights the low quality of the manuscript since the journal editor stated interest in this area of research (SAED_SEPT222021_SUPPL_000069). It is likely that these editors recognized that the inappropriate dose issue cannot be remedied in Dr. Saed's manuscript because repeating his experiments at physiologically relevant concentrations (which have not been reported in the literature) would likely not generate any responses, and his laboratory funding may depend on generation of "positive" results. In fact, the most recent version of his manuscript indicates that "A portion of Dr. Saed's time conducting this research was paid for by the lawyers representing plaintiffs in the talcum powder litigation" (Harper et al., 2021).

A select collection of reviewer comments included:

- "several critical fatal flaws" (SAED_SEPT222021_SUPPL_000101)
- "highly questionable" (SAED_SEPT222021_SUPPL_000101)
- "Based on the minimal amount of data provided in this manuscript, the authors' conclusions suggesting acute exposure of talc powder to ovary epithelial cells is associated with ovarian cancer are outrageous and not supported by the manuscript's data." (SAED_SEPT222021_SUPPL_000101)
- "this paper is written in such a manner that the science cannot be trusted" (SAED_SEPT222021_SUPPL_000102)
- "the transformation conclusion based on the results from unclear methodology is highly worrisome" (SAED_SEPT222021_SUPPL_000102)
- "Where is the explanation that these doses are even relevant for the exposure model?" (SAED_SEPT222021_SUPPL_000103)
- "all relevant information is missing" (SAED_SEPT222021_SUPPL_000103)
- "WST-1 is normally used for viability, It is unclear how this played a role in identifying malignancies" (SAED_SEPT222021_SUPPL_000103)
- "I have no idea what I am reading here ... This is very poorly explained" (SAED_SEPT222021_SUPPL_000103)
- "I did not see any carcinogenic assays" (SAED_SEPT222021_SUPPL_000103)
- "The problems with this submission are too numerous to count, and the science, methodology, and data cannot be trusted." (SAED_SEPT222021_SUPPL_000104)
- "The findings still would not establish that it is biologically plausible that talc causes ovarian cancer in living humans" (SAED_SEPT222021_SUPPL_000128)

- "Injection of talcum powder into the reproductive systems of laboratory animals to see if the same changes occur is highly recommended" (SAED_SEPT222021_SUPPL_000128)
- "What [is] the justification for the talcum powder amount added to cell cultures" (SAED_SEPT222021_SUPPL_000128)
- "Of primary concern is the reliance on a single commercial assay for assessment of transformation that has not been established in the literature" (SAED_SEPT222021_SUPPL_000069
- "The results of this study are over-interpreted" (SAED_SEPT222021_SUPPL_000070)
- "These data are too premature for publication" (SAED_SEPT222021_SUPPL_000070)
- "...the dose of talcum powder is extremely high" (SAED_SEPT222021_SUPPL_000070)

In summary, based on the numerous methodological flaws, misinterpretation of results, and overstatement of conclusions, the work of Dr. Saed and colleagues should be questioned when considering any relevance to the carcinogenic potential of talc and association with ovarian cancer.

In addition to Dr. Saed, other plaintiffs' experts, including Drs. Plunkett and Carson and many others similarly rely upon the findings from mechanistic studies conducted *in vitro* to support their opinions regarding biological plausibility, dose-response, and the alleged carcinogenic potential of talc, and development of ovarian cancer (Plunkett 11/15/2023; Cote 11/15/2023; Clarke-Pearson 11/15/2023; Levy 11/15/2023; Singh 11/15/2023; Smith-Bindham 11/15/2023; Wolf 11/15/2023). While the above described *in vitro* studies have examined aspects of gene expression changes, oxidative stress, inflammation and cell transformation, the inherent limitations of these studies need to be recognized particularly when the findings are considered in the context of negative carcinogenic data from animal toxicity studies involving talc. One of the major limitations of these *in vitro* studies and subsequently any conclusions drawn from such studies is the lack of information related to relevance of dose. As noted in the discussion of Dr. Saed's work above, the concentrations of talc used in each study appeared to be chosen based on testing increasing concentrations until a desired effect was observed. None of the described in vitro studies provided rationale to support the levels of talc used in the experimental system to physiologically-relevant doses in animals or humans. This approach is inherently unscientific since all substances exhibit toxic effects with a sufficiently high dose. Even if all other aspects of the study had been performed in an appropriate manner, using a dose that is much higher than a reasonable estimate of human exposure is misleading and does not retain any relevance to humans. As discussed previously in this report, there is no direct evidence from experimental animal or human studies that talc is capable of migrating to the ovaries following perineal exposure. Thus, any level of exposure *in vitro* would be considered unrealistic and inappropriate.

Further, the results from *in vitro* studies focus on changes during a short period of time (e.g. hours to days) during which cells are viable in culture. These results are not indicative of longer term changes, such as chronic inflammation, that plaintiff experts have proposed to play a role in development of ovarian cancer. Mechanistic studies are important for identifying underlying changes leading to a toxicological effect in animals and/or humans. However, in the case of talc and talcum powder, the toxicological evidence from various experimental animal and genotoxicity studies does not suggest carcinogenic potential. The few studies that do purport to

demonstrate changes in inflammation and gene expression related to carcinogenesis are flawed both in terms of methodology and overinterpretation of results. Therefore, the relevance of such studies to humans and in particular their usefulness is informing human health risk is limited.

For all of these reasons, the results presented in the various *in vitro* studies were lacking information related to relevance of dose, inconsistent, non-specific to carcinogenesis, and contrary to genotoxicity findings and results from animal toxicity studies.

10.1.8 Consensus Statements from Government and Scientific Agencies

Over the past several decades, several scientific and regulatory agencies have evaluated the available scientific evidence regarding a potential association between cosmetic talc, and perineal use specifically, and the development of ovarian cancer. In general, these agencies have noted weak, if any, associations and determined that evidence was lacking to conclude that there is a causal relationship.

In 1995, Carr et al. reported on the *Workshop on Talc* sponsored by the International Society of Regulatory Toxicology and Pharmacology (ISRTP), the Cosmetic, Toiletries, and Fragrances Association (CTFA), and USFDA. In the evaluation of the association between talcum powder use and ovarian cancer, the panel stated that "epidemiologic data are conflicting and remain equivocal. Although it is theoretically possible that talc could reach the ovaries, the actual access to or the presence of talc in ovarian tissue is not documented" (Carr, 1995, p. 215)

In 2010, IARC classified perineal use of talcum powder as "possibly carcinogenic to humans (Group 2B)" (IARC, 2010, p. 412). The IARC Monograph indicated that this determination was based upon "limited evidence" of carcinogenic potential for perineal use of talcum powders in humans, while noting potential confounding factors, bias, and inconsistent exposure-response data and "limited evidence" in experimental animals (IARC, 2010, p. 412) In the case of inhalation, IARC determined that talc not containing asbestos or asbestiform fibers was "not classifiable as to its carcinogenicity (Group 3)" (IARC, 2010, p. 412).

The Food, Drug and Cosmetic Act of 1938 established regulatory authority over cosmetic products by the Food and Drug Administration (USFDA, 2016). According to the Act, cosmetics are defined as products or components of products "intended to be rubbed, poured, sprinkled, or sprayed on, introduced to, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance" with the exception of soap (US Code, 2016). As such, talc-containing products, including various talcum powders, makeups, and deodorants, have been and are subject to regulation by the FDA. As stated in the Act, the FDA is responsible for ensuring that "cosmetics are safe and properly labeled" (US Code, 2012). In 2014, the FDA responded to two citizen petitions from 1994 and 2008 requesting that labeling of talcum powders be required to warn consumers of an increased risk of developing ovarian cancer with regular perineal use (Musser, 2014). In the response denying the petitions, the FDA indicated that, following a review of available scientific information, the agency "did not find … conclusive evidence of a causal association between talc use in the perineal area and ovarian cancer" (Musser, 2014, p. 1). FDA noted several limitations in the available

epidemiologic data including lack of exposure characterization, selection bias, uncontrolled confounding factors, inconsistent findings of positive association, and lack of a cogent biological mechanism. Importantly, the FDA also noted that a recent, large prospective cohort study published since IARC's evaluation in 2010, found no association between talc use and ovarian cancer.

In 2015, the Cosmetic Ingredient Review (CIR) published a safety evaluation for the use of talc in cosmetics (Fiume et al., 2015). The CIR panel concluded that talc was "safe for use in cosmetics in the present practices of use and concentration" (Fiume et al., 2015, p. 665). With regard to the potential association between perineal use of talcum powder and ovarian cancer, the panel stated that the available studies "do not support a causal link" (Fiume et al., 2015, p. 122S)

As previously described, Wentzensen and O'Brien, researchers at the National Cancer Institute (NCI) and National Institute of Environmental Health Sciences (NIEHS), respectively, reported a weak association between genital talc use and ovarian cancer risk in women with patent reproductive tracts – and no significant association overall – following review of recent epidemiological data. Notably, the authors stressed the need for further research given the lack of understanding for causal factors contributing the observed weak association (Wentzensen & O'Brien, 2021).

The National Cancer Institute (NCI) recently updated its Physician Desk Query (PDQ), an information resource provided for health professions. Perineal talc use was listed as a "[f]actor with inadequate evidence of an association risk of ovarian, fallopian tube, and primary peritoneal cancer" (NCI, 2023). A brief discussion noted the inconsistency of results among case-control and cohort studies, leading to the conclusion that "[t]he weight of evidence does not support an association between perineal talc exposure and an increased risk of ovarian cancer" (NCI, 2023).

Similarly, the American College of Obstetricians and Gynecologists (ACOG) noted limitations among the studies reporting associations between talc use and ovarian cancer. While recommending against the use of talc-based vaginal treatment due to "potential discomfort and pain," ACOG concluded that "there is no medical consensus that talcum powder causes ovarian cancer" (ACOG, 2017). Moreover, use of talcum powder products is not listed as a risk factor for ovarian cancer by the ACOG, nor the CDC (ACOG, 2022; CDC, 2023).

In April 2021, Health Canada issued a screening assessment for talc focusing on consumer exposures from talc-containing personal care products (Health Canada, 2021). Health Canada's assessment relied to a significant extent on expert reports from litigation. With regard to perineal talc exposure, Health Canada concluded that a review of epidemiological literature "indicate[d] a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer" (Health Canada, 2021, p. iii). When viewed in the context of Bradford Hill guidelines, Health Canada concluded that "the available data are indicative of a causal relationship" (Health Canada, 2021, p. 36). Health Canada's assessment relied on consideration of only four Hill criteria (strength, consistency, biological gradient, and biological plausibility) and did not address the other five considerations deeming them "to be less significant, or to hold less weight" (Health Canada, 2021, p. 29).

Interestingly, Health Canada noted that "significant exposure information [was] lacking" among the available literature to assess biologic gradient, one of the factors considered to hold more weight (Health Canada, 2021, p. 33). Health Canada's assessment also recognized lack of consistency across case-control and cohort studies, as well as among available data towards tumor subtype and potential for bias among study types. In addition, while Health Canada stated that epidemiological evidence showed a "consistent and statistically significant positive association," they also acknowledged that approximately one-half of case-control studies and all of the cohort studies did not demonstrate statistical significance (Health Canada, 2021, p. iii). Health Canada's conclusion regarding biological plausibility and the potential for talc-induced inflammation contributing to ovarian cancer development, is in part reliant upon on the studies of Fletcher et al. (2019) and Mandarino et al. (2020). The conclusions drawn from such *in vitro* studies needs to be closely evaluated in the context of human relevance or other study limitations, as I have previously described. In summary, the conclusions drawn by Health Canada are unsupported by the scientific literature as they are based on limited evaluation of the full breadth of available information and Bradford Hill guidelines.

10.1.9 Weight of Evidence and Consideration of Bradford Hill Guidelines

My own assessment, when viewed in the context of the Bradford Hill guidelines, is in agreement with the general consensus of the authorities listed above and contrary to the questionable conclusions of Health Canada:

Strength – The size of the reported increase in risk for ovarian cancer among perineal talc users is very small. The only studies that found an association between talc use and ovarian cancer (i.e., a subset of case-control studies) generally reported a weak association between perineal talc use and ovarian cancer risk. Risk ratios in these instances were approximately 1.2 to 1.6 versus controls, compared to the increased risk of lung cancer in cigarette smokers of 20 to 30 times that of the general population in the example used by Hill (1965). The weakness of the reported association is important because weak associations are more likely to be the result of bias or confounding.

Consistency – Consistency is lacking generally across study types. This is prevalent in population- and hospital-based case-control studies, as well as within population-based studies, many of which did not have statistically significant observations. There is also a lack of consistency between case-control and cohort studies, and in results among application scenarios (e.g., talc applied to perineum and talc applied to diaphragm).

Specificity – The evidence does not suggest that talc causes disease in a specific population or a specific type of disease. Although some studies have reported a higher association for African American than Caucasian women, the differences do not appear large enough or pervasive enough in the literature to make the specificity consideration strongly point to causation. Moreover, African American women are at a lower risk of ovarian cancer than white women as a general matter. In addition, there is no consensus as to associations of talcum powder use when stratified by histologic type of ovarian cancer.

Biological Gradient – Precise quantitative data related to exposure are not available on women's talc use. The fraction of reviewed studies that did attempt to capture data relevant to dose-response did so using imprecise estimates of frequency of use, duration of use, and/or total number of applications, largely based on study participants' memory (which could introduce significant bias). These factors create challenges when considering dose-response. In any event, many of the epidemiology studies that used imprecise proxies for talc exposure did not show a clear dose-response. Given the fundamental importance of dose in toxicological and risk assessment, the general lack of support cautions against inference of a causal relationship.

Temporality – The fact that talc use is reported to have preceded the onset of ovarian cancer in the case-control studies that reported a weak association is unsurprising. Based on the inherent retrospective study design, a temporal association is the only finding these studies could have possible reached. Cohort studies, which are generally considered stronger evidence of temporality based upon their prospective study design, did not find any significant association. Moreover, given that women typically reported that they began using talc at relatively young ages and that ovarian cancer is a disease that typically appears relatively later in life (irrespective of talc use), the basic temporal relationship reflected in these studies is far more likely to reflect correlation than causation.

Plausibility – An association between talcum powder exposure and ovarian cancer has not been corroborated by toxicological evidence. First, no studies have directly demonstrated migration of talc following perineal application to the ovaries. As noted earlier, animal studies in which talc was directly introduced into the female reproductive tract (e.g., vaginal and uterine applications) or via inhalation did not provide evidence for translocation to the ovary. In addition, the presence of talc particles in ovarian tissue alone, reported in some studies, could reflect contamination rather than migration, and is not supportive of causation. It is important to recognize that talc particles have been found in ovarian tissue in women with or without a history of perineal talcum powder application. All of this is consistent with IARC's conclusion that "the evidence for retrograde transport of talc to the ovaries in normal women is weak," and studies in animals showed no evidence of retrograde transport (IARC, 2010).

Further, even if talc were able to migrate to the ovaries following perineal exposure, for which there is limited to no evidence, talc has not been shown to be carcinogenic across several species and routes of exposure in animals. This is particularly evident in those studies that examined ovarian cancer incidence and/or pathological response of ovarian tissue in response to talc. The NTP (1993) study, which exposed animals to talc via inhalation, showed mixed evidence of carcinogenicity, but had numerous methodological problems as explained above. Nonetheless, no increases in ovarian lesions in talc-treated animals were observed in this study. Further, cellular experiments have not found cosmetic talc to be genotoxic. The several experimental *in vitro* studies that reported cellular toxicity and/or changes purportedly indicative to carcinogenesis from talc produced unreliable findings due in part to significant methodological flaws and possess little human relevance in the context of studies in experimental animals due to lack of consideration of physiologically-relevant doses.

Coherence – There is no coherence with the broader scientific understanding of carcinogenesis. If talc were toxic and carcinogenic, its alleged migration through the female reproductive system to the ovaries would be expected to generate an increased risk of other gynecologic cancers. Yet there is no consistent evidence of this. While some cohorts have found a positive association with talc use and uterine cancer (O'Brien et al., 2019) and endometrial cancer specifically (Karageorgi et al., 2010), other studies and reviews did not find an association with uterine/endometrial cancer (Crawford et al., 2012; Neill et al., 2012; O'Brien et al., 2021; Wentzensen & O'Brien, 2021) and endometrial cancer specifically (Crawford et al., 2012; Karageorgi et al., 2010; O'Brien et al., 2021; Wentzensen & O'Brien, 2021). The fact that studies of miners and millers of cosmetic talc, who face the highest levels of exposure, do not show an increased risk of any cancer also strongly indicates a lack of coherence.

Experimental evidence – Some reports have hypothesized about inflammation and oxidative stress having a carcinogenic role for talc, but there is a lack of toxicological and epidemiological evidence supporting that hypothesis. As described previously, associations between ovarian cancer and use of anti-inflammatory drugs or pelvic inflammatory disease (PID) are inconsistent or not established. Therefore, even if talc were able to migrate to the ovaries and induce inflammation following perineal exposure, there is no evidence that inflammation can cause ovarian cancer. Further, follow-up studies of patients receiving pleurodesis treatment undermine this theory. Pleurodesis involves the instillation of cosmetic (pharmaceutical) grade talc directly into the pleural space for treatment of pleural effusion. Despite the acute inflammatory reaction produced by the introduction of high doses of talc, a recent analysis found no mesotheliomas among patients with up to 40 years of follow-up (Finley et al., 2017). Finally, studies purporting to show that talc exposure causes oxidative stress or other *in vitro* markers of carcinogenesis (i.e., Dr. Saed's research) are highly flawed and uninformative with regard to human ovarian cancer risk.

Analogy – As demonstrated, there exists a substantial record of scientific literature for talc. Therefore, evidence drawn from similar substances or class of substances is less relevant than in instances where data are lacking. For this reason, relying upon data from one or more alleged accessory components (i.e., asbestos), which would represent an extremely small fraction of talc (e.g., <1%), even if it were present, is unnecessary. Dr. Plunkett and other plaintiffs' expert used asbestos as an analogous substance known to be a human carcinogen. Specifically, Dr. Plunkett made comparisons of adverse effects with asbestos and talc, stating that "[i]f a fiber is long, immune cells cannot totally engulf the compound and remove the foreign materials from the tissue" (Plunkett 6/20/2021: p. 20). While fiber length plays an important role in fiber toxicity, other factors, including durability, biopersistence, surface reactivity, and other size properties (e.g., width, aerodynamic diameter) contribute to the varying toxicity among different fiber types. The available toxicological and epidemiological literature clearly demonstrates that talc is non-carcinogenic. A detailed discussion regarding potential associations between asbestos and ovarian cancer is provided in Section 10.0 below.

10.1.10 Causation Summary and Conclusions

In summary, a weight of evidence analysis pursuant to the Bradford Hill guidelines for general causation makes clear that the science does not support a conclusion that perineal talc causes ovarian cancer. This is consistent with the conclusions reached by several scientific and governmental agencies, as discussed above.

10.1.11 Response to Bradford Hill Guidelines Summary by Plaintiffs' Experts

In my review of the various reports from plaintiffs' experts in this litigation, I identified no fewer than ten that reported applying the Bradford Hill guidelines in some fashion to support a causative relationship between talcum powder and ovarian cancer (Drs. Carson, Clarke-Pearson, Cote, Kane, McTiernan, Moorman, Siemiatycki, Singh, Smith-Bindman, and Wolf). Across their various reports, plaintiffs' experts emphasize the importance of different criteria and oftentimes present a variety of interpretations of the same Hill considerations. For example. Dr. Smith-Bindman downplays the importance of several criteria (e.g., dose-response, specificity) in her initial assessment, going so far as to suggest the criterion of specificity is "meaningless" in a causation analysis (Smith-Bindman 11/15/2018: p. 39). She later noted in her amended report that the criteria for specificity and dose-response were supported by the available data (Smith-Bindman 11/15/2023). Meanwhile, Dr. Carson stated that he "gave the most weight" to evidence supportive of the strength, consistency, and biological plausibility criteria (Carson 11/16/2018: p. 10). While Hill acknowledged in the original publication that all criteria may not be met during evaluation, he stated "all of which we should study" (Hill, 1965, p. 299).

Many of the plaintiffs' experts characterize the strength of association as "strong" or "extremely strong" (Carson 11/16/2018: p. 9; Smith-Bindman 11/15/2018: p. 37). This misrepresents the scientific literature, because the size of the reported association in the subset of studies that have found an association is objectively low (approximately 1.2 to 1.6). Dr. Carson refers to the association as "strong" without defining the magnitude of the association, which suggests that he has not truly analyzed this consideration (Carson 11/16/2018: p. 9). Dr. Carson agreed in his deposition testimony that a relative risk of approximately 1.3 (as calculated by other researchers), if correct, was indicative of a weak or modest association (Carson 12/19/2019: p. 232-233). This directly contrasts with Dr. Carson's characterization of the data supportive of a "strong" association. In addition, Dr. Carson's assertion that a 30% increased risk would result in a substantial number of preventable deaths is irrelevant to the application of the Bradford Hill guidelines (Carson 12/19/2019: p. 233). Dr. Carson also states that the "heavy majority" of case-control studies reported a "positive and significant" odds ratio, thus supporting a "strong association" for perineal talcum powder use and ovarian cancer (Carson 11/16/2018: p. 9). Several of the plaintiffs' experts reach similar conclusions based upon a purported majority of studies demonstrating increased risk. As I have described in my discussion of epidemiological studies, there is a considerable, if not equal, number of studies that have demonstrated no increased risk or a non-significant increased trend. In any event, these considerations relate to consistency, not strength. Overall, plaintiffs' experts' characterization of the association as "strong" contrasts with conclusions from other scientific and/or regulatory assessments as previously described, which have found inadequate evidence or generally weak associations.

The plaintiffs' experts also characterize the epidemiologic evidence as showing a consistent association. For example, Dr. Carson states that the "majority" of epidemiology studies reported a positive association between perineal talcum powder use and ovarian cancer (Carson 11/16/2018: p. 9). However, Dr. Carson later testified that this criterion should be evaluated by determining whether there is "consistency across different types of studies" (Carson 12/19/2019: p. 240). In both his expert report and deposition, Dr. Carson acknowledges that cohort studies have not demonstrated statistically significant associations (Carson 11/16/2018: p. 9; Carson 12/19/2019: p. 238). In doing so, Dr. Carson recognizes the lack of consistency in the epidemiological literature, and the interpretation as presented in his report is not consistent with Bradford Hill guidelines. Therefore, in stating that the majority of studies show increased risk, plaintiffs' experts have not considered and/or are misrepresenting the full set of evidence.

Dr. Carson's analysis of other Bradford Hill considerations is similarly incomplete. With respect to biological gradient, for example, Dr. Carson identifies several epidemiology studies that he claims showed a dose-response relationship between talcum powder exposure frequency and duration in certain subgroup analyses (Carson 11/16/2018: p. 9). However, he acknowledges the fact that the majority of studies show no clear dose-response (Carson 11/16/2018: p. 9). He also acknowledges that accurate quantitative data on talc dose is not available in the studies and appeared to assume without analysis that "simply multiplying" frequency and duration of talc use is a valid substitute (Carson 11/16/2018: p. 7), when in fact those metrics are highly imprecise as explained above.

Many plaintiffs' experts also rely upon potential mechanisms of toxicity that remain unproven and/or with questionable relevance in humans. For example, Dr. Carson states in his report that toxicological studies showed that talc caused cancer following administration to experimental animals (Carson 11/16/2018: p. 4). However, Dr. Carson does not provide any reference for this statement; nor does he acknowledge the numerous animal studies utilizing multiple routes of administration and species, as I have previously discussed, which have not found any evidence of tumors following talc treatment. Dr. Carson also characterizes talcum powder as "a complete carcinogen" based primarily on *in vitro* evidence of an inflammatory response following talc treatment (Carson 11/16/2018: p. 5). Complete carcinogens are substances capable of inducing all carcinogenic stages, including "initiation, promotion, and progression and hence by definition have genotoxic properties" (Klaassen, 2013, p. 398). However, based on negative findings in various assays, it is the general scientific consensus that talc is not genotoxic (Fiume et al., 2015; Goodman et al., 2020; IARC, 2010; USEPA, 1992). Dr. Carson's assertion regarding the carcinogenicity of talc: (1) does not consider the limitations of extrapolating from *in vitro* data, (2) does not consider the greater evidence from animal and human studies, and (3) is not consistent with scientific and toxicological principles for analysis of the potential for carcinogenicity.

In summary, the analysis and conclusions towards causation made by plaintiffs' experts are flawed, inconsistent with scientific approaches, and contradictory with the general scientific community.

10.2 Specific Responses to Expert Report of Laura M. Plunkett, Ph.D., DABT, dated June 30,

2021

10.2.1 Dr. Plunkett's Failure to Conduct a Proper Risk Assessment Including Lack of Consideration of Dose

Dr. Plunkett states that she used the process of human health risk assessment as a means to conduct a safety assessment of the carcinogenic potential of talcum powder (Plunkett 6/30/2021: p. 7). In her report, she purportedly provides evidence for the toxicity of talcum powder and its constituents, including talc, asbestos, heavy metals, and fragrance chemicals. She opines that the weight of evidence demonstrates that "genital exposure to talcum powder products increases the risk of ovarian cancer in women" (Plunkett 11/15/2023: p. 58). However, Dr. Plunkett testified at her deposition that she did not perform an analysis for general causation (Plunkett 8/10/2021: p. 107).

One of the major flaws in Dr. Plunkett's report and her subsequent conclusions is her failure to properly conduct a risk assessment. As I have previously stated in my report, risk assessment is built on the framework of four basic steps as recommended by the National Academy of Sciences including: (1) hazard identification, (2) dose-response assessment, (3) exposure analysis, and (4) characterization of risk (NRC, 1983). Each of these four steps is critical to the process and one or more steps cannot be excluded. Dr. Plunkett's approach is flawed in that she fails to address the steps of dose-response assessment and exposure analysis. With regard to dose-response, Dr. Plunkett states that "weight-of-the-evidence methods were critical to defining the literature that identified the hazards of talc exposure as well as defining the dose-response relationship between talc exposure and the risk of adverse health effects;" however, the very next sentence in her report indicates that she was "not attempting to define any specific exposure in quantitative terms" (Plunkett 11/15/2023: p. 8). Instead, Dr. Plunkett considered the evidence for a dose-response relationship between talc and ovarian cancer from the available epidemiology, animal toxicity, and *in vitro* studies (Plunkett 11/15/2023: p. 55). As I have previously discussed, the doses/concentrations used in the described *in vitro* studies did not have any physiological basis, therefore the observance of a dose-response in these studies is not meaningful in the context of risk assessment. In addition, Dr. Plunkett makes reference to the NTP animal study for evidence of a dose-response effect in terms of talc toxicity and carcinogenic effect in rodents (Plunkett 11/15/2023: p. 55). A previously noted, the tumors observed in rats in this study were likely due to excessive exposure to talc resulting in lung burden overload. For this reason among others, an expert panel in 1994 stated that the NTP study "has no relevance to human risk" (Musser, 2014). Furthermore, Dr. Plunkett fails to acknowledge that despite the observed lung and adrenal gland tumors observed in rats, there were no observed pathological changes between controls and talc-treated rats (Boorman & Seely, 1995). Therefore, Dr. Plunketts' reliance on various *in vitro* and animal toxicology studies to support her conclusions on dose-response are misleading and do not take into account physiologically-relevant doses for humans.

In addition to her flawed conclusions on dose-response, Dr. Plunkett does not attempt to identify a specific exposure/dose of talcum powder association with development of ovarian cancer. This step is critical in any risk

assessment to identify the quantitative relationship between exposure and adverse effects that can be applied when examining a specific exposure scenario (e.g. exposure assessment), such as perineal exposure via talcum powder.

Further, Dr. Plunkett stated that she did not "define any specific exposure in quantitative terms"; instead, she reportedly conducted an exposure assessment with respect to "the relevant routes of human exposure that would be relevant for evaluating the risks posed by use of the powders" (Plunkett 11/15/2023: p. 8). This approach of identifying relevant routes of human exposure is an inherent piece of the first step of hazard identification that is used to define the potential of a substance to cause harm to human health. An understanding of the route of exposure to a substance (i.e., oral, inhalation, dermal) is a critical component in determining relevant hazards. While Dr. Plunkett identifies talc and other constitutents of talcum powder (e.g. asbestos, fibrous talc, heavy metals, fragrance chemicals) are carcinogens and/or toxic agents, she does not consider the potential degree of exposure and subsequent doses that an individual might experience during use of talcum powder products. This is an inherent flaw in Dr. Plunkett's "risk assessment," since without a consideration for exposure to these substances, one cannot develop conclusions regarding risk.

In summary, Dr. Plunkett fails to: (1) identify a dose of talcum powder associated with development of ovarian cancer; or (2) estimate an exposure resulting from perineal use of talcum powder. The latter is in part likely due to the absence of quantitative exposure data related to perineal applications in the scientific literature. Without adequate consideration of these critical steps, Dr. Plunkett provides an incomplete and flawed risk assessment, and any conclusions from this unscientific approach must therefore be questioned.

10.2.2 Dr. Plunkett's Inconsistency in Recognizing a Threshold for General Carcinogenicity

Dr. Plunkett states that "talc may be a non-genotoxic carcinogen," which she defines as an agent that "is not a direct mutagen, exhibits a threshold for tumor development, produces tumors that exhibit a dose-response relationship with exposure … and may exhibit species, strain, and tissue specificity in response" (Plunkett 11/15/2024: p. 51-52). While non-genotoxic carcinogens do exhibit a threshold, to say that talc is a carcinogen of any sort is completely speculative and not supported by weight-of-evidence from epidemiological and toxicological data. She also acknowledged in her deposition testimony that non-genotoxic carcinogens are "assume[d]" to possess a threshold dose below which there would be no carcinogenic activity (Plunkett 12/19/2018: p. 281, p. 282, l. 9). However, she later testified at her deposition that she was unable to identify a threshold dose for potential carcinogenicity of talc related to ovarian cancer (Plunkett 12/19/2018: p. 282). Dr. Plunkett's failure to consider dose or identify a threshold dose is not consistent with standard methodologies and scientific principles underlying carcinogenicity and risk assessment.

11.0 ASBESTOS

Asbestos is the name given to a number of naturally occurring fibrous minerals with high tensile strength, the ability to be woven, and resistance to heat and most chemicals. Because of these properties, asbestos fibers

have been used in a wide range of manufactured goods, including insulation, roofing shingles, ceiling and floor tiles, paper and cement products, textiles, and coatings. There are two basic forms of asbestos: serpentine (chrysotile) and amphibole (crocidolite, amosite, anthophyllite asbestos, tremolite asbestos, and actinolite asbestos). Each form has defined physical and chemical characteristics.

11.1.1 Drs. Longo and Rigler's Estimate of Potential Asbestos Exposure from Use of Johnson's Baby Powder and Shower to Shower

Drs. Longo and Rigler issued a report that included MAS's laboratory data on 58 historical cosmetic talcum powder products (both Johnson's Baby Powder and Shower to Shower) dated from the 1960s through the 2000s (Longo & Rigler, 2019). Of the 58 examined samples, two were later identified as from the same product bottle (M68233-001 and M68233-002), two samples were identified as amphibole-containing during analysis conducted by Lee Poye but were not confirmed by MAS, and seven bottles came from Asian markets not intended for distribution in the US market. Therefore, quantitative amphibole content via TEM analysis was available for 48 US-market historical samples. Just 28 of the 48 samples were reported to contain amphiboles by MAS. Of those 28 samples reported to contain amphibole fibers/bundles, the reported concentrations ranged from 8,360 to 268,000 fibers/bundles per gram of talc, with an average of approximately 25,000 fibers/bundles per gram (Longo & Rigler, 2019).

Based on the bulk sample analysis, Drs. Longo and Rigler opined that users of historical talcum powder products "would have, more likely than not, been exposed to significant airborne levels of … regulated amphibole asbestos" (Longo & Rigler, 2019, p. 32). This statement is scientifically unjustified for two reasons. First, extrapolation of airborne exposure concentrations based upon bulk content is not a standard practice of industrial hygiene and exposure assessment. One also needs to consider the amount of a hazardous substance that is available for exposure, in this case, how much may be liberated into the air during use and available to be inhaled. Simply relying upon bulk content is not sufficient to extrapolate to potential exposure. Second, Drs. Longo and Rigler provide no indication of what they consider a "significant" exposure. In the fields of toxicology and risk assessment, a significant exposure can be defined as that capable of producing a dose that leads to an adverse health effect or development of disease. Importantly, exposure intensity, frequency of use, and duration of use are important considerations when evaluating exposure. Drs. Longo and Rigler fail to consider any of these factors when referring to a 'significant' exposure.

For the purposes of this report, I have calculated an airborne exposure based upon the bulk analysis data presented by Drs. Longo and Rigler and made comparisons to relevant exposure concentrations considered protective of human health. As the first step of this analysis, I determined an estimate of airborne fiber concentrations associated with talcum powder use based upon the bulk analysis presented by Drs. Longo and Rigler. Several studies have evaluated airborne dust exposures in persons using talcum powder products under a variety of conditions, including 1) infant exposure during diapering, 2) adult exposure during application to infant during diapering, and 3) personal application to face or body (Anderson et al., 2017; Aylott et al., 1979; Moon et al., 2011; Rasmussen et al., 2019; Russell et al., 1979).

Specifically, several have reported short-term airborne dust concentrations, or total mass of particles in the air regardless of shape or composition (mg/m^3), associated with talcum powder use summarized in **Table 3**, below.

Table 3: Summary of Airborne Dust Data from Talcum Powder Exposure Studies

Study Reference	Details of Use	Sampling Details (Application time/Duration)	Sample Number (n)	Mean Airborne Concentration (mg/m^3)
Aylott et al., (1979)	Face powder using puff applicator	Application time: 16-19 sec Sampling time: 5 min	16	0.48
	Body application	Application time: 27-31 sec Sampling time: 5 min	35	1.13
	Infant diapering	Application time: 2.9-3.3 sec Sampling time: 5 min	32	0.21
Russell et al., (1979)	Body application	Application + Sampling time: 1.23 min	44	2.03
	Infant diapering	Application + Sampling time: 0.53 min	48	0.19
Moon et al., (2011)	Infant diapering	Application time: 30 sec Sampling time: 5 min	10	0.022
	Adult during infant diapering	Application time: 30 sec Sampling time: 5 min	10	0.005
Anderson et al., (2017)	Body application	Application time: 13-47 sec Sampling time: 48 min	20	1.46
Rasmussen et al., (2019)	Body application	Application time: 57 sec Sampling time: 0.95 min	3	1.58

Study Reference	Details of Use	Sampling Details (Application time/Duration)	Sample Number (n)	Mean Airborne Concentration (mg/m^3)
	Face powder using puff applicator	Application time: 47 sec Sampling time: 1.1 min	2	1.8
	Application while donning wet suit	Application time: 192 sec Sampling time: 11.7 min	3	0.61

Using the above data on dust exposures (mg/m^3), the bulk fiber concentrations reported by Drs. Longo and Rigler (f/g) can be converted to an estimated airborne fiber concentration (f/cc). I have calculated exposures under an average and worst-case scenario using average and maximum values from the exposure studies and Drs. Longo and Rigler's bulk analysis using the following equation:

> Airborne fiber exposure (f/cc) =
> average/maximum airborne dust concentration (mg/m^3) * average/maximum amphibole asbestos in bulk sample (structures/g of talc) * conversion factor (1 m^3 air / 1,000,000 cc air)

Table 4: Estimated Airborne Fiber Exposures Based Upon Bulk Analysis Data from Dr. Longo and Rigler

Scenario	Airborne Dust Concentration (mg/m^3)	Bulk Amphibole Asbestos (structures/mg talc)[c]	Estimated Airborne Fiber Exposure (f/cc)
Average Exposure	2.03[a]	25	***0.00005***
Maximum Exposure	5.03[b]	268	***0.0013***

[a] Highest reported average airborne dust concentration across studies (Russell et al., 1979)
[b] Single highest reported airborne dust concentration across studies (Anderson et al., 2017)
[c] As reported by Drs. Longo and Rigler in analysis of historical cosmetic talcum powders.

The average and maximum airborne concentrations of asbestos associated with talcum powder use based upon bulk analysis data reported by Drs. Longo and Rigler were ***0.00005 f/cc*** and ***0.0013 f/cc***, respectively. It is important to recognize that these concentrations are based on short-term sampling of airborne concentrations as occurs during application of talcum powder products over the course of several minutes. Therefore, it is necessary to consider these short-term exposures in the context of long-term or chronic exposures particularly when considering the relevance to asbestos-related diseases.

11.1.2 Comparison to Estimated Asbestos Exposures to Ambient Airborne Levels

Everyone living in the United States is exposed to background levels of asbestos due to both human activity and natural sources. Background exposure to asbestos can result from the presence of asbestos-containing materials in urban and rural environments (Abelmann et al., 2015; Churg & Warnock, 1980; Commins, 1989; Doll, 1987; HEI, 1991; Mangold, 1983; Nicholson et al., 1980). Other exposures to low levels of asbestos may occur: (1) in buildings that contain asbestos-containing materials; (2) near busy traffic areas or highways; (3) in the ambient air of urban cities; (4) and in rural areas (HEI, 1991; WHO, 1998a). ATSDR (2001) reported that typical indoor and outdoor air concentrations of asbestos are approximately 10^{-4} f/cc (0.0001 f/cc), as measured by PCM, with higher values reported in the vicinity of exposure sources. ATSDR (2001) stated that the range of asbestos

concentrations "likely to be encountered in ambient, nonoccupational outdoor or indoor air" was $3x10^{-6}$ to $6x10^{-3}$ f/cc (p. 44). A review article published by Abelmann et al. (2015) determined overall mean and median ambient asbestos concentrations in the US from the 1960s to 2000s of 0.0002 and 0.00009 f/cc, respectively, with a range of detected values of 0.000005 to 0.05 f/cc. It is important to recognize that exposures to ambient air occur 24 hours per day, 365 days per year over a person's lifetime. Therefore, over the course of a 70-year lifetime and assuming an average ambient concentration of 0.0001 f/cc, an individual experiences an estimated cumulative exposure to asbestos of **0.007 f/cc-years** from breathing ambient air.

Unlike continuous exposure to ambient air, hypothetical exposures to asbestos resulting from talcum powder depend upon an individual's usage habits but are typically limited to a few minutes per day during specific periods of one's lifetime. Thus, in addition to intensity, frequency and duration of use are critical in determining one's potential exposure to asbestos from talcum powder. I have calculated a lifetime cumulative exposure for talcum powder using conservative estimates, that is likely to overestimate an individual's lifetime exposure. This estimate is based upon exposure to the average and maximum airborne fiber concentrations (0.00005 and 0.0013 f/cc, respectively) based upon the claimed findings of Drs. Longo and Rigler in Johnson's Baby Powder, with an exposure duration of 30 minutes per day (assuming multiple uses per day), and exposure frequency of 365 days per year for 70 years.

> Cumulative Lifetime Exposure (f/cc-year) =
> (Exposure Intensity (f/cc) * Exposure Duration [min]) * (1 hour / 60 min) * (365 days / 1 year) * 70 years / (8760 hours / year)

The estimated average and maximum cumulative exposures to asbestos from talcum powder using the above equation are **0.000073 f/cc-years and 0.0019 f/cc-years**, respectively. These values are approximately 4 to 100 times less than the estimated cumulative exposure to asbestos from ambient air. Therefore, based ondose-response principles, potential exposure to asbestos from talcum powder would not increase the risk, if any exists at all, of developing ovarian cancer or any other asbestos-related disease versus that associated with ambient air.

11.1.3 Risk Characterization of Ambient Asbestos Exposures

Price and colleagues have studied the incidence of asbestos-related disease, including mesothelioma, related to low level exposures seen in the environment that would affect the whole US population (Price, 1997, 2004; Price & Ware, 2004). The authors demonstrated that age-adjusted rates of mesothelioma in US females from 1973 to 2000 were constant despite significant changes in asbestos usage and ambient asbestos concentrations during this time (Abelmann et al., 2015; Price & Ware, 2004). Similarly, age-adjusted pleural mesothelioma rates in US males correspond with historical asbestos consumption rates, while neither trend is observed with mesothelioma in women (Moolgavkar et al., 2009, 2017). More recently, Glynn et al. (2018) showed that age-adjusted rates of pleural mesothelioma were similar in women from urban versus rural US regions, despite an approximate 10-fold or greater ambient asbestos concentration in urban settings. These studies demonstrate

that (1) a threshold exists for asbestos below which one would not expect to see an increased risk for mesothelioma, and (2) low concentrations of asbestos in the ambient environment are not associated with increased incidence or risk of mesothelioma.

In 1985, the FDA convened the Quantitative Risk Assessment Committee to conduct an analysis of the potential added cancer risk in humans from any potential exposure to asbestos in cosmetic talc (Brown, 1985). Specifically, the committee evaluated the potential exposure to asbestos experienced by an infant resulting from regular talcum powder applications during diaper changing over a period of two years. One of the critical pieces of the FDA's risk assessment was the assumption that cosmetic talc contained 0.1% anthophyllite or tremolite asbestos. This assumption was reportedly based upon recent analysis and samples tested by the FDA (Brown, 1985). The exposure estimate conducted by the committee demonstrated that infant exposure to asbestos was significantly lower ($0.3x\ 10^{-6}$ times) than that experienced by asbestos workers examined in epidemiological studies. The committee concluded that the "added human risk of lung cancer and mesothelioma from possible asbestos in talc is less than 10^{-8} lifetime risk and quite possibly orders of magnitude less" (Brown, 1985, p. 11). Further assessment noted that mothers (or other applicators) may also be exposed during application of talcum powder to infants, but their risk "should be relatively smaller" as they were likely to experience less exposure compared to infants during application (Brown, 1985, p. 5). In the petition denial issued in 1986, the FDA noted that this risk was less than that associated with lifetime environmental background (ambient) exposures to asbestos (Swanson, 1986).

Recently, Burns et al. (2019) performed an updated analysis of the FDA risk assessment based upon additional exposure information for talcum powder application available from several of the exposure studies described above (Anderson et al., 2017; Aylott et al., 1979; Dement et al., 1972; Gordon et al., 2014; Hildick-Smith, 1976; Moon et al., 2011; Russell et al., 1979). Assuming an asbestos content of 0.1%, the authors determined that risk associated with cumulative exposures experienced during the evaluated scenarios of use (infant and adult exposure during diapering of an infant, adult exposure from body and face powdering) were within or below acceptable levels established by USEPA's non-occupational asbestos risk assessment. Similar to the 1985 FDA risk assessment, cumulative exposure and risk were found to be below that associated with exposure to asbestos at environmental background (ambient) levels (Burns et al., 2019).

The conclusions reached by these risk assessments are consistent with toxicologic and epidemiologic data that demonstrate no increased risk of mesothelioma development with exposure to cosmetic talc.

11.1.4 Epidemiology Studies of Asbestos and Ovarian Cancer

A number of studies and reviews have examined occupational exposures to asbestos and development of ovarian cancer in women.

In 2012, IARC reviewed 11 cohort studies of 13 populations, ten with occupational exposure and three with community-based exposure, to examine the association between asbestos exposure and ovarian cancer. IARC

concluded that "a causal association between exposure to asbestos and cancer of the ovary was clearly established, based on five strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos" (IARC, 2012b, p. 256). IARC also recognized three studies involving community-based environmental asbestos exposure as additional support for its conclusion, although each of these studies showed a non-significant increase in ovarian cancer mortality or incidence (Ferrante et al., 2007; Reid et al., 2008, 2009). When considering the possibility that cases of peritoneal mesothelioma were misclassified as ovarian cancer, IARC noted that of the three studies that reviewed the potential for misdiagnosis, they failed to identify a sufficient number of misclassified cases (IARC, 2012b).A recent cohort study by Dalsgaard et al. (2022) of women exposed to environmental asbestos as school children in Denmark found a non-significant decrease in ovarian cancer incidence compared to the control population, despite significant increases in mesothelioma and lung cancers (when adjusted for smoking via COPD status).

Click or tap here to enter text.In connection with the IARC Working Group, Camargo et al. (2011) conducted a meta-analysis of 18 cohort studies to examine the incidence of ovarian cancer among women with occupational asbestos exposure. The industries involved in the meta-analysis were mining and the manufacture of asbestos-containing products. The authors reported an association between asbestos exposure and the development of ovarian cancer among the pooled estimate. A statistically non-significant association was found when the authors looked at specific types of asbestos, with crocidolite and mixed asbestos exposure cohorts displaying higher SMRs than chrysotile alone (Camargo et al., 2011). To adjust for the potential misclassification of peritoneal mesotheliomas, the authors repeated the meta-analysis after removing 20% of ovarian cancer cases from each study, citing the estimation that 16% of peritoneal cases were misdiagnosed as ovarian cancer. The authors reported that "it would seem unlikely that the association between occupational asbestos exposure and ovarian cancer could be fully explained by tumor misdiagnosis" (Camargo et al., 2011, p. 1216).

Bunderson-Schelvan et al. (2011) performed a literature review of the non-pulmonary effects of asbestos exposure. The authors reported that a number of epidemiological studies found a weak association between ovarian cancer and asbestos exposure, but few reached statistical significance. They also noted the potential for the misclassification of peritoneal mesothelioma as ovarian cancer. The authors concluded that "more studies are required to solidify the concerns regarding asbestos and ovarian cancer" (Bunderson-Schelvan et al., 2011, p. 135).

In 2011, Reid et al. performed a literature review meta-analysis of 14 cohort and two case-control studies to examine the relationship between asbestos exposure and ovarian cancer. Four of the cohort studies reported a statistically significant positive association between asbestos exposure and the development of ovarian cancer. The authors concluded that "taken without further analysis, women thought to have ovarian cancer had an increased rate in the meta-analysis if reporting having been exposed to asbestos, compared with reference populations. This result may have occurred because of disease misclassification [of peritoneal mesothelioma]" (Reid et al., 2011, p. 1287). Although, the positive association no longer appeared when only those studies with pathological confirmation of ovarian cancer were considered, suggesting a strong potential of misclassification

in earlier studies. The authors also noted that IARC's classification was "premature and not wholly supported by the evidence," in part due to a lack of consistency among dose-response and risk across the available epidemiological studies (Reid et al., 2011, p. 1294).

Nowak et al. (2021) more recently conducted a meta-analysis of available studies through 2016 as part of the designation of ovarian cancer due to asbestos exposure as an occupational disease in Germany. The authors reported an approximate doubling of SMR (1.88; 95% CI 1.47-2.39) across all studies. Similar results were observed if distinctions were made for ovarian cancers with or without histological confirmation. Turati et al. (2023) reported similar results in their meta-analysis (SMR = 1.79; 95% CI 1.38-2.31) with higher risk ratios reported in association with amphibole exposures compared to chrysotile-only exposed occupational cohorts.

A recent review paper highlighted the lack of consistency in asbestos/ovarian cancer studies (Slomovitz et al., 2020). The authors also explained that the studies IARC relied on potentially misclassified other disease (i.e., peritoneal mesothelioma) as ovarian cancer and thus may not have reported accurate data on ovarian cancer incidence. These studies did not generally verify diagnoses with pathological testing, and limited pathological verification has suggested a misclassification rate of over 25 percent. Slomovitz and colleagues also noted that the IARC Working Group's conclusion that there was a causal association between asbestos and ovarian cancer was primarily established based on five cohort studies "with heavy occupational exposure to asbestos" (Slomovitz et al., 2020, p. 4). Furthermore, the authors noted that the IARC Working Group also "reviewed several papers that showed a non-significant risk of ovarian cancer due to asbestos exposure, but these were not included in the consensus opinion" (Slomovitz et al., 2020, p. 5). The authors concluded that the association between asbestos and ovarian cancer was "weak and inconsistent" with further investigation required (Slomovitz et al., 2020, p. 6).

To summarize, any conclusions regarding an association between ovarian cancer and asbestos exposure have primarily relied on occupational cohorts. IARC and others noted that studies cited as strongly supporting the conclusion that there was a causal relationship between asbestos exposure and ovarian cancer were all composed of women who experienced heavy occupational exposure. Studies that reviewed female cohorts who were non-occupationally or environmentally exposed to asbestos did not report a statistically significant association with ovarian cancer. In addition, misclassification of other malignancies as ovarian cancer may have biased the results of studies that reported an association. Further, exposure information is lacking among nearly all of the occupational and non-occupational studies examining the potential association between asbestos exposure and ovarian cancer. For these reasons, IARC's conclusions on this issue were premature and not supported by the available evidence. Furthermore, if there is a causative relationship between asbestos exposure and ovarian cancer, it is only in cases of heavy occupational exposure to asbestos. As I have demonstrated above, any potential exposure to asbestos from talcum powder use is less than, or at most comparable to, breathing ambient air which has not been associated with increased risk of asbestos-related disease. Therefore, the potential levels of asbestos to which one may be exposed from use of talcum powders

is not comparable to the occupational exposures considered in the studies reviewed by IARC and do not present an increased risk of ovarian cancer.

11.1.5 Fibrous/Asbestiform Talc

Drs. Longo and Rigler reportedly identified the presence of fibrous talc in their bulk analysis of Johnson's Baby Powder and Shower to Shower and concluded that "significant" exposure to fibrous talc would occur during consumer use of such products (Longo & Rigler, 2019).

In addition to the platy form, talc may also exist in a fibrous morphology. The term fibrous describes mineral particle(s) occurring in bundles of fibers, consisting of a group of individual long, thin crystals (Campbell et al., 1977). Because of the different physical characteristics imparted by platy versus fibrous particles, fibrous talc is not typically present at significant levels, if at all, in cosmetic talc products. As a result, the reported identification of fibrous talc in cosmetic talc preparations should be carefully considered. In the talc monograph published in 2010, IARC stated that "[t]alc particles are normally plate-like. When viewed under the microscope in bulk samples or on air filters, they may appear to be fibres and have been identified as such" (IARC, 2010, p. 277). In addition, the term "fibrous talc" is often confused with "asbestiform talc." Asbestiform is a description applicable to all minerals based on a pattern of growth or habit that results in "fibres that are very long and thin and occur in parallel bundles that are easily separated from each other by hand pressure" (Campbell et al., 1977; IARC, 2010, p. 277) In particular, IARC stated that the term "asbestiform talc has erroneously been used for talc products that contain asbestos," as well as "erroneously been used for talc products that contain elongated mineral fragments that are not asbestiform" (IARC, 2012b, p. 230).

Further, in IARC's 2012 publication of asbestos, the agency stated:

> "*For talc that contains asbestiform fibres, previous Working Groups assessed studies on talc described as containing asbestiform tremolite and anthophyllite (IARC, 1987a, b). These fibres fit the definition of asbestos, and therefore a separate review of talc containing asbestiform fibres was not undertaken by this Working Group*" (IARC, 2012b, p. 234)

This distinction is critical since IARC's assessment does not indicate that talc itself, even if occurring in an asbestiform habit, is carcinogenic. Various epidemiological and toxicological assessments have concluded that fibrous talc possesses far less toxicity, if any, compared to asbestos fibers (Garabrant & Pastula, 2018; Smith et al., 1979; Stanton et al., 1981; Wylie et al., 1997). Dr. Plunkett seemed to recognize this in her deposition when she acknowledged that she did not hold the opinion that fibrous talc has the same toxic potential as tremolite (Plunkett 12/19/2018: p. 151).

In summary, the weight of evidence suggests that fibrous talc does not cause asbestos-related cancers. The reported identification of fibrous talc by Drs. Longo and Rigler in Johnson's Baby Powder is therefore irrelevant to the evaluation of ovarian cancer risk. If fibrous talc were present in cosmetic talc preparations at sufficient

levels to cause asbestos-related disease, it would be reflected in the various epidemiological and toxicological studies of talc that I have previously described.

11.1.6 Summary

Positive associations between asbestos and ovarian cancer are only observed in cases of heavy occupational exposure that are not relevant under consumer use conditions. Hypothetical exposures resulting from the use of Johnson's Baby Powder and Shower to Shower based upon bulk analysis data presented by Drs. Longo and Rigler are less than historical concentrations of asbestos present in ambient air in the US. Low concentrations of asbestos, such as those occurring in ambient air, are not associated with the risk for developing asbestos-related diseases, including ovarian cancer. The relevant scientific literature does not support a causal association between fibrous talc and asbestos-related cancers nor ovarian cancer. Finally, plaintiffs' experts' reliance of the classification of asbestos as an ovarian carcinogen does not include a consideration of dose. Thus, extrapolation of evidence from heavy occupational exposures as purporting causation between talcum powder and ovarian cancer is not consistent with principles of general causation and risk assessment.

12.0 HEAVY METALS

Heavy metals are ubiquitous in the environment and humans are exposed to these compounds in the daily course of eating, drinking, breathing, and physical contact with the environment. Non-occupational estimates of heavy metal intake from food and water have been reported by several agencies including the USFDA and ATSDR (ATSDR, 2005, 2007a, 2007b, 2012a, 2012b). While some metals have been characterized as carcinogenic in humans, there are two important considerations for examining the ability of heavy metals in talcum powder to cause ovarian cancer. First, evidence of carcinogenicity with respect to specific tissue does not make it appropriate to extrapolate that a metal is also carcinogenic with respect to another tissue or cancer type, such as ovarian cancer. None of the metal constituents reported in talcum powders have been causally associated with ovarian cancer. Second, the classification of carcinogenicity for multiple metals is typically based upon high exposures experienced in occupational settings. These types of exposures are generally confined to workers manipulating materials on a daily basis and would not be representative of exposure through routine use of consumer products. These considerations are discussed in further detail in the following sections.

12.1 Heavy Metals and Cosmetic Talc and Talcum Powders

Talc, like many other natural products derived from the earth and soil, is known to contain a range of certain metals, with concentrations varying significantly based on many factors, including the source and state of processing (i.e., raw ore or finished baby powder). Metals are not intentionally added to talcum powders such that any metals present in finished products is inherent to the mined product, as is the case for most naturally-occuring minerals. Few studies have been published that report concentrations of heavy metals in cosmetic talc products (Cralley et al., 1968; Rehman et al., 2013). Cralley et al. (1968) examined the presence of metals, albeit using an unreported detection method. With the exception of three products, 19 of the tested products

contained the following metal concentrations (or lower): cobalt <25 ppm, chromium <22 ppm, and nickel <29 ppm.

Dr. Plunkett opines that "evidence shows that the products manufactured by Imerys and sold by Johnson & Johnson contained detectable levels of heavy metals" (Plunkett 6/30/2021: p. 24). Even if true, this is not unexpected given that talc is a mineral-based material, and soil and rocks contain various levels of heavy metals. Dr. Plunkett also states that "[t]he levels of heavy metals have varied across different processed lots of talcum powders, but internal company documents show that certain heavy metals have been repeatedly detected, such as chromium (Cr), cobalt (Co), and nickel (Ni)" (Plunkett 6/30/2021: p. 25). However, she fails to mention that one of the most important reasons that metal levels have varied across samples is due to talc sample type, including results reported for talcum powders as well as raw ore samples. Similarly, Drs. Cook and Krekeler cited documents reporting or discussing results for heavy metal testing of multiple talc product samples. These Imerys and Johnson & Johnson results, as discussed in the expert reports of Dr. Mark Krekeler (Krekeler 11/16/2018) and Dr. Robert Cook (Cook 11/16/2018), are summarized in **Table 5** below.

Table 5: Summary of Heavy Metal Testing Results of Imerys and Johnson & Johnson Documents

	Heavy Metals (ppm)[a]		
Product Tested	**Total Chromium**	**Total Cobalt**	**Total Nickel**
Baby Powder	ND – 400	0.0 – 66	30 – 2,050
Other Samples	0.25 – 8,500 (<4 – 70 ppb Cr [VI])	0.1 – 96	<0.2 – 2,650

[a] *As cited by Dr. Krekeler and Dr. Cook. All values presented in ppm (ppm = mg/kg)*
ND = not detected; NR = nor reported

Results shown in **Table 5** indicate a range of values for the identified heavy metals in talc samples, with concentrations spanning two to three orders of magnitude. The variation in concentrations within the samples that Drs. Cook and Krekeler cite, and to which Dr. Plunkett refers, was likely the result of multiple factors, including type of talc samples, state of refinement, and source location and date. For example, the other samples in the analysis included not only baby powder samples, but also various talc and talc drill samples, talc of different grades and processing states, mine sludge, rock, aerosol, and other samples from varying locations. In addition, crude talc ore, which was reported to contain the highest concentrations of metals, cannot be directly compared to the final product, which has undergone processing via magnetic separation and acid washing steps to remove metals and other natural mineral components (Fiume et al., 2015).

It is important to note that metals present in talc are generally bound into the lattice structure of the talc particle, which prevents their release and potential interaction as free metals in solution or ability to exert a biological action (CIR, 2013). Testing has been performed by Johnson & Johnson to understand whether and to what extent metals present in talc samples are not bound to the particle structure (i.e., extractable, not bound in the lattice structure). A Johnson & Johnson memo from 1976 indicated that a small proportion of nickel (30 ppm), cobalt (4 ppm), and chromium ("a few ppm") found in a lot of Johnson's Baby Powder was observed in "non-talc components" versus the amount of metal bound in the talc molecular lattice (JNJ000246467). Another memo from 1976 reported on an experiment involving the extractability of metals from Johnson's Baby Powder subject to biological fluids for up to 14 days. The percent of extractable metal versus total metal present in the sample was found to be "extremely low," ranging from 0.30 – 1.2% for chromium, 0.22 – 1.2% for cobalt, and 0.16 – 0.48% for nickel (JNJ000238011: p. 7). The available evidence indicates that the vast majority of metals present in talcum powder are trapped by way of chemical bonds in the talc structure and, thus, only a very small portion is potentially biologically available (i.e., extractable or non-talc components). Therefore, the relevant or biologically available portion of any reported levels of metals in Johnson's Baby Powder and Shower to Shower products is substantially less than the total amounts reported.

Although Dr. Krekeler indicates in his report that Chinese talc contained "higher than normal heavy metal contents, like lead, cobalt, chromium, iron, nickel and titanium" (Krekeler 11/16/2018: p. 11), Dr. Cook contradicts this by stating that "[a]nalyses of Chinese talc ores consistently indicate very low concentrations of heavy metals (IMERYS 225295) with As, Co, Cr, and Ni values often at or below 1.2 ppm, 2.7 ppm, 4.0 ppm and 4.6 ppm, respectively (IMERYS 058214 at 226) in 2009 for example" (Cook 11/16/2018001, p. 27). Dr. Krekeler also cites a document reporting that chromium (assumed total chromium) levels present in talc samples ranged from 1.6 - 5 ppm (JNJ000059273. p. 9, 11, 18). Total chromium levels in US soils range from 1 to 2000 ppm (ATSDR, 2012a), which indicates that reported levels for talc samples are quite low in comparison. As soils and minerals naturally contain varying amounts of metals, the study described in this document was important to understand the composition of the talcs present at the site. This resulted in a recommendation to mine the white talc, which was described as cosmetic grade, rather than the gray or green talcs, which naturally contained more metals (JNJ000059273).

To properly interpret any potential risk to human health associated with metals present in talc, one must recognize that the general population is frequently exposed to each of the heavy metals at issue on a regular basis as a result of simply being in the environment (e.g., breathing air, eating food, drinking water). Plaintiffs' experts consistently fail to acknowledge such environmental exposures nor do they consider how any potential exposure to metals from perineal talcum powder use compare to such exposures and potential resulting health effects. This is a critical error and indicates that their conclusions are deeply flawed. For example, Dr. Plunkett stated that "[t]hese heavy metals are known to be toxic to human cells and tissues" but does not consider the doses at which this toxicity might occur, which is surprising since she is a toxicologist and should be very cognizant that dose is a key part of any risk assessment (Plunkett 6/30/2021: p. 25). In addition, although many of the plaintiffs' expert contend that heavy metals present in Johnson & Johnson talcum powders contribute to

the development of ovarian cancer, none even considers whether or how a reported level of the discussed metal in talcum powder may lead to an exposure capable of causing ovarian cancer (or any type of cancer, for that matter). Therefore, there is no scientific evidence to support the claim that heavy metals in talc products are causally associated with or contribute to the development of ovarian cancer.

Furthermore, Dr. Plunkett, along with other plaintiffs' experts, highlights the carcinogenic classification for each metal, but fails to provide information regarding the type of cancer that has been associated with the metals in humans or animals, or the dose at which that effect could occur (e.g., Plunkett 6/30/2021: p. 25).

Below I discuss each of the heavy metals allegedly present in cosmetic talc: chromium, cobalt, and nickel. I also address plaintiffs' experts' claims regarding each of these metals.

11.1.1 Chromium

Chromium's valence, or oxidation, state (i.e., the number of valence electrons in the outer shell of the chromium atom) dictates the toxicokinetic disposition and potential carcinogenicity of chromium. Chromium (Cr) exists in multiple forms (the most common valence states are Cr[0], Cr[III], and Cr[VI]) and occurs naturally in rocks, plants, animals, and soil, and as a product of certain industrial processes (ATSDR, 2021a). Chromium [III], the most stable valence state conformation, is an important element in the body and is the form that is far more likely to be found in rocks and similar materials, such as talc.

Chromium is widely distributed in air, water, soil, and food. Chromium [III] occurs naturally and is a normal part of the human diet for which recommended daily intakes have been established. Meanwhile chromium [VI], also known as hexavalent chromium, and the less common elemental chromium [0], are most commonly produced by industrial processes (IOM, 2001; USEPA, 2000a). Chromium [VI] compounds generated during manufacturing possess a range of structural conformations and differ in solubility. Erosion of natural chromium deposits can also give rise to chromium [VI] (USEPA, 2021a); however,its natural occurrence is rare (USEPA, 1984).

In the general population, exposure to chromium occurs by inhaling ambient air, consuming food or water containing chromium, or via dermal contact with some consumer products and soils containing chromium. Of these potential exposure routes, ingestion of chromium with food is the most substantial source for the general population (ATSDR, 2012a). The USEPA National Drinking Water Standard for total chromium (including chromium [VI]) is 0.1 mg/L, or 100 ppb (USEPA, 2021a). Given that the average individual consumes two liters (L) of water per day, ingestion from water at the standard alone would be 0.2 mg (200 µg). Intake of chromium from dietary supplements most commonly ranges from 35-120 µg, but it is also found in supplements at concentrations as high as 1000 µg, or 1 mg (NIH, 2021a). Combined with food/beverage intake, daily intake levels can easily exceed this amount. Ingestion of chromium-containing foods is the main source of chromium exposure in the general US population, for which the ATSDR estimates the mean dietary intake is 35.35 µg/day (based on an average 70 kg adult) (ATSDR, 2012a). According to the WHO (2003), food contains <10 – 1300 µg/kg chromium, in which the highest concentrations have been detected in meat, fish, vegetables, and fruit. The

Institute of Medicine Food and Nutrition Board has not established an upper limit for chromium since it concluded that no adverse effects have been linked to high intakes (IOM, 2001).

Occupational exposure to chromium is primarily associated with chromate production and plating, stainless steel production and welding, production of ferrochrome alloys and chrome pigments, and working in tanning industries (Ashley et al., 2003 as cited by ATSDR, 2012a). Inhalation of vapors and particulates laden with chromium [VI] are the primary methods of occupational exposure to chromium.

Chromium is important in the digestion of fats and carbohydrates, stimulation of fatty acid and cholesterol synthesis (which is essential for adequate brain function and other body processes), and aids in the balance of glucose and insulin action (USNLM, 2021a). For adults, the Institute of Medicine (IOM) has recommended a daily intake of 20-45 µg/day based on age, gender, and pregnancy/lactation status (with highest requirement for lactating females) (NIH, 2021a). Because chromium [III] is poorly absorbed by any exposure route, the toxicity of "chromium" is mainly attributable to the chromium [VI] form. This may be because when chromium [III] enters the bloodstream, cellular transport mechanisms in humans have been shown to deny its entry into the cell (Norseth, 1986).

According to IARC, "[t]here is inadequate evidence in humans for the carcinogenicity of metallic chromium and of chromium [III] compounds" (IARC, 1990a, p. 213). The USEPA has rated chromium [III] as "Group D -- Not classified as to its human carcinogenicity" based on inadequate data and the National Toxicology Program (NTP) has only evaluated chromium [VI] (NTP, 2016; USEPA, 1998a). According to ATSDR and IARC, animal studies on chromium [III] do not provide evidence to support a carcinogenic rating (ATSDR, 2012a; IARC, 2012a). Chromium [III] carcinogenicity ratings from these agencies are included in **Table 6**, below.

Table 6: Carcinogenicity Ratings for Chromium [III]

Agency	Ratings
IARC	Group 3 - Not classifiable as to its carcinogenicity to humans
USEPA IRIS	D – Not classifiable as to human carcinogenicity
NTP	NA

IARC has rated chromium [VI] compounds as "Group 1 - Carcinogenic to humans" based on increased risk for lung cancer (IARC, 2012a). The USEPA determined that inhalation of chromium [VI] is associated with an elevated risk for lung cancer (USEPA, 2021e). In addition, the NTP indicated that chromium [VI] compounds are known to be human carcinogens based on sufficient evidence from studies in humans showing an increased for respiratory tract cancer (primarily lung cancer) (NTP, 2016). Ratings for carcinogenicity of chromium [VI] are included in **Table 7**.

Table 7: Carcinogenicity Ratings for Chromium [VI]

Agency	Ratings
IARC	Group 1 - Known Human Carcinogen

USEPA IRIS	A – Carcinogenic to Humans
NTP	Known to be a Human Carcinogen

Importantly, my review of the literature identified no mechanistic or epidemiologic studies that established a causal relationship between any type of chromium exposure, including chromium [VI], and ovarian cancer.

12.1.1 Response to Chromium-Related Opinions from Plaintiffs' Experts

- **Expert Report of Robert B. Cook, PhD, dated November 16, 2018**

Dr. Cook acknowledges that at least two forms of chromium (chromium [III] and chromium [VI]) exist but fails to consider that one form is considered carcinogenic, while the other is intentionally ingested as a dietary supplement (Cook 11/16/2018: p. 30). Dr. Cook also admits that the ratio of these two chromium forms has not been determined in chlorites, the mineral he reported as being present in some talc samples (Cook 11/16/2018: p. 32). However, it has been reported that "apart from the rare mineral crocoite ($PbCrO_4$) all naturally occurring chromium is found in the trivalent state" (Ebdon et al., 2001, p. 315), which is important since this mineral is never mentioned in Dr. Cook's report.

There are multiple issues and errors in the talc sample results that Dr. Cook included in the table of his chromium section (Cook 11/16/2018: p. 30-31). He does not report which chromium valence state was detected, in that total chromium or a non-specified form of chromium was reported in most cases according to the laboratory reports he cites (JNJ000063608; JNJ000239730). He also reports at least one value in the table that was unadjusted for the blank sample concentration (JNJ000246437).

Dr. Cook states that "regardless of valence," the Grade 66 Imerys samples consistently contain chromium levels above the 5 ppm chromium limit (Cook 11/16/2018: p. 32), although it is not clear what this reported limit is derived from, which valence state it applies to, or what the purpose would be since FDA does not have a limit for chromium in cosmetics, even those products to be applied to the eyes or other mucous membranes, which contain talc (USFDA, 2022).

Dr. Cook also misrepresents several of the documents he cites by stating that "[i]nternal documents outline J&J's concern regarding the potential carcinogenic nature of Cr(VI)" (Cook 11/16/2018: p. 32). For example, Dr. Cook cites a Johnson & Johnson memo from March 8, 2010 (JNJ000131758), which states that the analytical method used for specification limits in talc sample measured total chromium. However, the document explains that even if a conservative assumption was made that 100% of the chromium in the talc was in the form of chromium [VI], this would still result in an exposure level that is one-fifth of the Safe Harbor Value established under California Prop 65 regulations for chromium [VI] for an adult exposure scenario and 1/200 to 1/300 of the Safe Harbor Value for exposure scenario involving an infant (JNJ000131758, p. 3). Further discussion in another set of Johnson & Johnson documents that Dr. Cook cites (JNJ000131761) indicated that talc samples meeting specification limits (7 ppm), even assuming that all chromium occurs in the chromium [VI] form, would result in an airborne concentration that is far below exposure limits designed to protect workers exposed all day long in

occupational settings. In the cited documents it is apparent that there was a misunderstanding of the laboratory results and applicable specification limits for chromium, which created some discussion between affected parties. Dr. Cook states that there is discussion in this document of raising the 7 ppm specification limit for chromium (Cook 11/16/2018: p. 32); however, I was unable to locate that point in the document provided. The previously discussed document (JNJ000131758) discusses raising the limit from 0.5 to 7 ppm, which as earlier mentioned, would conservatively assume that all chromium measured was in hexavalent form and would result in exposures associated with product use that were compliant with California Proposition 65 regulations for chromium [VI]. Therefore, Dr. Cook's suggestion that internal Johnson & Johnson documents highlight "concern" for chromium [VI] found in talcum powder is factually incorrect.

Dr. Cook also focuses on the concentration of total chromium (i.e., no indication of chromium [III] or chromium [VI]) in the samples he reported (Cook 11/16/2018: p. 30-31); however, these concentrations should only be considered relevant if used as part of an exposure/dose reconstruction as part of a risk assessment to determine whether the exposure level was consistent with studies that showed development of ovarian cancer. In the case of chromium, regardless of chromium [III] or chromium [VI] form, no level of exposure has been reported to cause ovarian cancer. Thus, any argument regarding bulk concentration of chromium in talc is unfounded. Finally, chromium is commonly found in the environment from natural and anthropogenic sources; thus, any additional contribution from exposure to talc is of questionable significance.

Finally, although Dr. Cook mentions that chromium [VI] has been rated as carcinogenic by IARC (Cook 11/16/2018, p. 30), he fails to mention that the rating is based on increased incidence of lung cancer, not ovarian cancer.

- **Expert Report of Mark Krekeler, PhD, dated November 16, 2018**

Dr. Krekeler indicates that "Chinese talc contains higher than normal heavy metal contents, like lead, cobalt, chromium, iron, nickel and titanium" (Krekeler 11/16/2018: p. 11). In the samples described in the document he cites, chromium (assumed total chromium) levels ranged from 1.6 - 5 ppm (JNJ0059273). As previously noted, total chromium levels in US soils range from 1 to 2000 ppm (ATSDR, 2012a).

Similar to Dr. Cook, Dr. Krekeler also fails to differentiate between chromium [III] and chromium [VI] in the sample results he provided (Krekeler 11/16/2018: p. 32-33). This was reportedly due to the inability of laboratory methods used to differentiate the valence state. Although he mentions chromium under his "Toxic Metal Contamination" section of his report (Krekeler 11/16/2018: p. 36-37), Dr. Krekeler failed to consider the valence state, which is critical in terms of toxicological potential.

Dr. Krekeler also acknowledges that chromium [VI] has been classified as carcinogenic by IARC (Krekeler 11/16/2018: p. 36), but like Dr. Cook and others, he neglects to mention that the rating is based on increased incidence of lung cancer, not ovarian cancer.

- **Other Plaintiffs' Experts**

In addition to Drs. Cook and Krekeler, other plaintiff experts including Plunkett, Carson, and Smith-Bindman also fail to consider the difference in potential toxicity and carcinogenicity between the two major forms of chromium (chromium [III] and chromium [VI]) (Plunkett 6/30/2021: p. 25; Carson 11/16/2018: p. 5-6; Smith-Bindman 11/15/2018: p. 5, 16). The general statements offered by these experts regarding the presence of chromium in talc without acknowledgement or determination of chromium [VI] levels render their opinions irrelevant from a toxicological perspective.

11.1.2. Cobalt

Cobalt naturally occurs in rocks, soil, water, plants, and animals. Cobalt, which may exist in a variety of forms, is used to produce alloys for aircraft engines, magnets, tools for cutting and grinding, artificial hip and knee joints, and colorants for glass, ceramics and paints (ATSDR, 2004). Cobalt is also released into the environment as a result of processes including cobalt mining, smelting, and processing/manufacturing of cobalt and cobalt-containing materials, fossil fuel combustion, and use of cobalt-containing fertilizers (ATSDR, 2004).

The general population is exposed to cobalt via inhalation of ambient air and ingestion of food and certain beverages including drinking water and beer. Cobalt is an essential trace element for humans, as it is incorporated as part of vitamin B12 and a variety of other co-enzymes known as cobalamins (Lindsay & Kerr, 2011). The recommended dietary allowance (RDA) for vitamin B12 is 2.4 µg/day, a dose that contains 0.1 µg cobalt (ATSDR, 2004), although the mean daily intake from food in the US has been estimated at up to ~12 µg/day based on the FDA Total Diet Study (Pennington & Jones, 1987). According to the NIH, about 29% of women reported using a dietary supplement containing vitamin B12, which also contains cobalt (NIH, 2021b).

Based on estimates from the Total Diet Study, an ongoing study that tracks intake levels of nearly 800 dietary nutrients and contaminants, average daily intake of cobalt ranges from 3.4 to 11.6 µg/day (assuming a 70 kg average adult body weight), with levels varying by age and gender. An average estimate of 11 µg cobalt is ingested daily according to ATSDR, with baked goods and cereals (29.8%) and vegetables (21.9%) categories of food groups contributing the greatest amounts (Dabeka and McKenzie, 1995 as cited by ATSDR, 2004). Surface and ground water cobalt concentrations usually average between 1-10 µg/L in cities and are less in rural areas (Hamilton, 1994; Smith and Carson, 1981 as cited by ATSDR, 2004). Results for average intake of cobalt by age group are provided in **Table 8**.

Table 8: FDA Average Daily Consumption of Cobalt by Age and Gender

Age	Cobalt(µg/day)[a]
6-11 Months	3.4

2 Years	5.2
14-16 Years	11.6 (M)/7.6 (F)
25-30 Years	10.8 (M)/7.2 (F)
60-65 Years	9 (M)/6.3 (F)

[a] *Based on FDA Total Diet Study as reported in Pennington and Jones (1987)*

Results from animal studies indicate no carcinogenic effect of cobalt in the ovary. Two cancer bioassay studies were conducted by the NTP in 1998 and 2014 showing that, although lifetime exposure (2 years) for 6 hr/day, 5 day/wk to cobalt sulfate (up to 3 mg/m^3) and cobalt metal (up to 5 mg/m^3) caused several neoplastic and non-neoplastic effects, no increased incidence of ovarian tumors was observed in either rats or mice (NTP, 1998, 2014). Injection site tumors were also reported in rats that received poorly water-soluble forms of cobalt; however, rats are susceptible to sarcomas following injection of a variety of substances. Several studies have noted various types of sarcoma (primarily rhabdomyofibrosarcoma, rhabdomyosarcoma, or fibrosarcoma) following intramuscular or intrathoracic injection of cobalt metal (Heath, 1956; Heath & Daniel, 1962; NTP, 2016) or cobalt nanoparticles (Hansen et al., 2006 as cited by NTP, 2016). However, as the NTP noted, studies that exposed animals to lower doses did not report tumors in the sites where tumors formed in other studies, indicating that there is a concentration threshold for toxicity (NTP, 2016).

The available human study data are not adequate to determine whether cobalt is a human carcinogen. As the NTP indicates in its 2016 report on cobalt, cohort studies reported an increased risk of lung cancer, and two case-control studies reported an increased risk of esophageal cancer, but it was not clear in any of these studies whether cobalt was the causal agent (NTP, 2016). In the studies reporting an increased risk of lung cancer, the NTP noted that workers were also exposed to known lung carcinogens, and in the studies reporting increased risk of esophageal cancer, exposure was only measured in the preceding 12-18 months via toenail clippings. Thus, it is not clear what role cobalt played in these studies.

Various forms of cobalt and cobalt-containing compounds/materials have been reviewed by multiple agencies to evaluate their carcinogenic potential. IARC has designated cobalt metals with tungsten carbide as “Group 2A - Probably Carcinogenic to Humans,” a designation associated with an increased risk for lung cancer, whereas cobalt metals lacking tungsten carbide, cobalt sulfate, and other soluble cobalt (II) compounds all have been designated as “Group 2B - Possibly Carcinogenic to Humans” due to associations with nasal/paranasal and lung cancers (IARC, 2018). However, based on the analytical results for talc that have been made available to me, cobalt with tungsten carbide is not a component of talc. A carcinogenic rating for cobalt has not been assigned by the USEPA (USEPA, 2021d). The NTP has evaluated “cobalt and cobalt compounds that release ions *in vivo*” and “cobalt-tungsten carbide: powders and hard metals” categories of compounds separately, both of which received a “Reasonably anticipated to be a human carcinogen” rating (NTP, 2009, 2016, 2021). However, cobalt-tungsten carbide is a synthetic material; it is likely not present in talc. Thus, the only relevant cobalt carcinogenicity ratings are for the Cobalt and Ion-Releasing Compounds category (Group 2B – Possibly Carcinogenic to Humans). A compilation of carcinogenicity ratings for these groups is included in **Table 9**.

Table 9: Carcinogenicity Ratings for Cobalt-Tungsten Carbide and Cobalt Compounds

Agency	Ratings	
	Cobalt and Ion-Releasing Cobalt Compounds	**Cobalt-Tungsten Carbide**
IARC	Group 2B - Possibly Carcinogenic to Humans	Group 2A - Probably Carcinogenic to Humans
USEPA IRIS	NA	NA
NTP	Reasonably Anticipated to be a Human Carcinogen	Reasonably Anticipated to be a Human Carcinogen

Since the last reviews of the potential carcinogenicity of cobalt by IARC and NTP, a 2021 systematic review and meta-analysis of 20 peer-reviewed papers on cobalt-containing orthopedic implants and 10 occupational cohort papers representing approximately one million individuals was published evaluating the association between overall cancer risk and cobalt exposure. Individuals were exposed to cobalt via orthopedic implants or cobalt particulates in occupational settings. The authors reported meta-analysis summary estimates for overall cancer risk of 1.00 (95% CI: 0.96–1.04) across all studies evaluated and 0.97 (95% CI: 0.94–1.00) among those considered high-quality, indicating no increase in overall cancer risk (Zhang et al., 2021).

Importantly, my review of the literature identified no mechanistic or epidemiologic studies that established a causal relationship between cobalt exposure and ovarian cancer.

12.1.2 Response to Cobalt-Related Opinions by Plaintiffs' Experts

- **Expert Report of Robert B. Cook, PhD, dated November 16, 2018**

Dr. Cook's discussion of cobalt levels found among talc samples is inconsistent both within his report and that of other plaintiffs' experts. For example, Dr. Cook notes that some talc samples have exceeded the 3 ppm upper limit for cobalt (Cook 11/16/2018: p. 33), although it is not clear where the limit value was derived. However, it was reported elsewhere (Dr. Krekeler's report) that "Johnson & Johnson established 10 ppm as the acceptable limit for the presence of cobalt in the talc ore." (Krekeler 11/16/2018: p. 37). Dr. Cook then states that cobalt concentrations ranged from 56 – 89 ppm in composite samples from 1974 and 2001, but his own table includes a 1996 composite sample that contained 8.1 ppm cobalt (Cook 11/16/2018: p. 33), which is much lower than his stated range. It is not clear whether this is the same composite sample that was tested using an alternate analysis method.

- **Expert Report of Mark Krekeler, PhD, dated November 16, 2018**

Dr. Krekeler reports that IARC classified cobalt as Group 2B (possibly carcinogenic to humans) but fails to state that this classification was associated with studies of respiratory tract cancer, not ovarian cancer (Krekeler 11/16/2018: p. 37). Regardless of the level of cobalt in the finished talcum powder product, no concentration of cobalt has been shown to cause ovarian cancer.

Dr. Krekeler claims that cobalt concentrations are elevated in talc samples (Krekeler 11/16/2018: p. 37). The three baby powder concentrations listed by Dr. Krekeler (50, 50, and 57 ppm; Krekeler 11/16/2018: p. 38) were derived from two reports (JNJ000087928 and JNJ000238011). In the first report, the number 50 appears in a handwritten note rather than typed with the original data. It is not fully clear which sample this value was associated with, and it seems quite possible that the data were not finalized since, aside from the fact that the data are handwritten, another field in that same row contains a question mark. Additionally, the data are not presented in uniform units (most values in ppm, some in %, one value is illegible) with regard to the handwritten portion of the document. Thus, I do not have confidence in this report, at least the handwritten portion, especially since the typed result for the Johnson's Baby Powder is 0.0 ppm cobalt. However, even if a sample of baby powder did contain 57 ppm cobalt by weight, this concentration in the bulk product is not concerning from a toxicological perspective.

Specifically, Dr. Krekeler states that source mines used for Johnson's Baby Powder and Shower to Shower products "contained excessive levels of cobalt" as compared to federal NIOSH and OSHA standards (Krekeler 11/16/2018: p. 37). OSHA, NIOSH, and ACGIH have established occupational airborne exposure limits for mixtures of cobalt fume and dust ranging from 20 to 100 ug/m^3 as an 8-hour time-weighted average. For comparison, studies of talcum powder application have reported mean airborne dust concentrations of 0.005 to 2.03 mg/m^3 (JNJ000131761; see previous discussion in Section 10.0). Based on a reported cobalt concentration of 57 ppm (57 µg cobalt per 1 g talc), and assuming an airborne dust concentration of 2.04 mg/m^3 during talcum powder application activities, the estimated airborne cobalt concentration is 0.12 ug/m^3. Assuming an exposure duration of 30 minutes per day (assuming multiple uses per day), this corresponds to an 8-hr TWA of 0.0075 ug/m^3, which is orders of magnitude less than occupational limits established for cobalt by OSHA or other agencies. Thus, chronic exposure to cobalt from talcum powder use is far below any occupational limits and would not be expected to be associated with any adverse health effects. Moreover, cobalt is not known to cause non-respiratory cancers. Thus, the relevant route of exposure for occupational standards is via inhalation, which is not relevant for alleged perineal exposure and potential associations with ovarian cancer. Thus, even if exposure to cobalt did occur from perineal use of talcum powders, ovarian cancer would not be an expected outcome.

11.1.3. Nickel

The WHO states that nickel is "present throughout nature and is released into air and water both from natural sources and as a result of human activity" (WHO, 2000). According to ATSDR, nickel is a "very abundant natural element ... found in all soil" (ATSDR, 2021b). In its pure form, it is described as silvery-white in color and hard, which is partly why it is used in many manufactured items such as jewelry, coins, stainless steel, and other alloys (ATSDR, 2021b). Nickel also forms various compounds with several oxidation states (although it is the divalent ion that is most common) and these compounds may be soluble or insoluble (WHO, 2000). Approximately 99% of nickel exposure is obtained from food and water sources, although the percentage drops to 75% in smokers (WHO, 2000).

The USFDA has indicated that the estimated average daily nickel intake is 68.8 to 162.5 µg/day, depending on age group and gender (**Table 10**). ATSDR reports that the intake of nickel per day for ingestion from food, drinking water, and breathing air is approximately 170 µg, 2 µg, and 0.1 to 1 µg, respectively (ATSDR). Foods that contain relatively high amounts of nickel include chocolate, soybeans, nuts, and oatmeal. The USFDA regulates nickel in bottled water and in pharmaceutical products. For bottled water, the permitted concentration is 100 ug/L (200 ug intake for an average intake of 2 L/day) and in pharmaceuticals, the levels for inhalation, injection, and oral routes of intake are 5, 20, and 220 ug/day, respectively (USFDA, 2022; USP, 2017). A permitted daily exposure level has also been established by the USFDA for trace nickel in pharmaceuticals. Results from the USFDA Total Diet Study for average intake of nickel by age group are provided in **Table 10**.

Table 10: FDA Average Daily Consumption of Nickel by Age and Gender

Age	Nickel(µg/day)[a]
6-11 Months	68.8
2 Years	90.4
14-16 Years	162.5 (M)/118.9 (F)
25-30 Years	146.2 (M)/106 (F)
60-65 Years	130.8 (M)/99.6 (F)

[a] *Based on FDA Total Diet Study as reported in Pennington and Jones (1987)*

Several scientific and regulatory agencies have evaluated the carcinogenic potential of nickel and its compounds. IARC has rated nickel compounds as a "Group 1 - Known Human Carcinogen" associated with an increased risk of lung cancer and nasal/paranasal cancer (IARC, 2018), although nickel compounds are not likely to be present in talc structure as the metal atoms are primarily bound within the lattice structure (CIR, 2013; JNJ000246467). For implanted foreign bodies consisting of metallic nickel, metallic cobalt, and metallic chromium, IARC has assigned a 2B rating – Possibly Carcinogenic to Humans. Additionally, IARC has also categorized metallic nickel as 2B rating – Possibly Carcinogenic to Humans. The USEPA has determined that insoluble nickel compounds (nickel refinery dust and nickel subsulfide) are carcinogenic in humans (USEPA, 2021e). In addition, the NTP has indicated that metallic nickel is reasonably anticipated to be a human carcinogen based on sufficient studies in animals, and it states in its reports that nickel compounds are known to be human carcinogens based on sufficient evidence from human studies (NTP, 2016).

Ratings for nickel and nickel compound carcinogenicity are provided in **Table 11**.

Table 11: Carcinogenicity Ratings for Nickel and Nickel Compounds

Agency	Ratings		
	Nickel Compounds	**Implanted Foreign Bodies with Metallic Nickel, Cobalt, and Chromium**	**Metallic Nickel**
IARC	Group 1 - Known Human Carcinogen	Group 2B – Possibly Carcinogenic in Humans	Group 2B – Possibly Carcinogenic in Humans
USEPA IRIS	A – Carcinogenic to Humans (refinery dust, nickel carbonyl, and nickel subsulfide)	NA	NA
NTP	Known to be Human Carcinogens	NA	Reasonably Anticipated to be a Human Carcinogen

A causal association between nickel exposure and ovarian cancer has not been established in the scientific literature. Although nickel was reported by one research group to accumulate in ovarian epithelial cells of ovarian cancer patients (Canaz et al., 2017), it is not possible to determine from the data made available in the paper whether the nickel contributed in some way to cancer development or whether the cancer cells accumulated a greater concentration of metals as a result of cancer cell dysregulation of metal homeostasis. The authors described an increased ability of cancer cells to indiscriminately accumulate nickel though multiple mechanisms, including the divalent metal transporter-1 (DMNT) protein. Moreover, the authors did not report any potential exposure details (concentrations, durations, frequencies) and did not consider other ovarian cancer risk factors. In humans, the highest amounts of absorbed nickel are found in the lungs, thyroid glands, and adrenal glands, with lesser amounts in the brain, kidneys, heart, liver, spleen, and pancreas (ECHA, 2018; Rezuke et al., 1987)

In its second addendum on nickel, the WHO cited the International Committee on Nickel Carcinogenesis in Man (ICNCM), which evaluated the carcinogenicity of different nickel species through analysis of 10 cohorts of workers occupationally exposed to nickel (ICNCM, 1990). The committee concluded that occupational exposure to high concentrations of sulfidic and oxidic nickel causes lung and nasal cancers; however, there was no correlation between metallic nickel exposure and cancer in lung or nose, which IARC also noted in its decision to classify metallic nickel as Group 2B (IARC, 1990b). The ICNCM indicated that exposure to soluble forms of nickel increased cancer risk. The Committee also found no substantial evidence that exposure to nickel compounds was associated with cancers other than in the lung or nose resulting from occupational exposures. The WHO reports that inhalation is an important route of exposure with regard to toxic effects, given the lack of evidence supporting carcinogenicity with oral exposure (WHO, 2007). According to the European Union (EU), many soluble and insoluble nickel compounds are classified as Carc 1A (known to have carcinogenic potential for humans); however, the EU has specified that inhalation leading to a risk of lung or nasal cancers is the only route of concern (ECHA, 2020). Therefore, it has not been established that nickel causes ovarian cancer.

In lifetime rodent studies (2 years, 6 hr/day, 5 d/wk with highest concentrations ranging from 0.5-2.5 mg/m^3), neither rats nor mice developed ovarian neoplasms when exposed to high or low solubility forms of nickel (nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate) (NTP, 1996a, 1996b, 1996c). Animal studies support the conclusions from human studies that the respiratory tract is the target area for nickel compound carcinogenesis, and the relevant exposure route by which this may occur is inhalation. Additionally, both human and animal studies support the absence of carcinogenic effects associated with nickel metal, while sulfidic and oxidic nickel compounds have led to carcinogenesis.

Dose is also extremely important in the determination of risk associated with nickel carcinogenicity. It has been reported that genotoxic effects of nickel compounds in the lung are observed following inflammation and macrophage activation that result in indirect oxidative DNA damage, although "the indirect genotoxic and non-genotoxic effects of nickel compounds have thresholds below which these effects are not observed" (Buxton et al., 2019). The only type of nickel-related cancer in humans (respiratory cancer) is associated with threshold levels of exposure below which no excess cancer risk has been reported. For example, inhalable aerosols did not cause excess cancer in 13 cohorts representing approximately 100,000 workers when concentrations were below 0.1 mg/m^3 (Buekers et al., 2015; Oller et al., 2014).

12.1.3 Response to Nickel-Related Opinions by Plaintiffs' Experts

- **Expert Report of Robert B. Cook, PhD, dated November 16, 2018**

Dr. Cook states in his report that he has seen "no evidence to suggest that Johnson & Johnson or Imerys ever planned or implemented a procedure for removal of nickel minerals from the talc ore." (Cook 11/16/2018: p. 28). However, early testing was performed by JNJ to determine whether the metals were available from the talc (JNJ000246467; JNJ000238011). Since only very low amounts were extractable, it would be logical to assume that removal was not necessary.

12.2 Summary

Based on my review of the heavy metals that have been reported as associated with Johnson's Baby Powder and Shower to Shower, namely chromium, cobalt, and nickel, it is clear that none of these metals has been associated with ovarian cancer at any dose, let alone any potential dose associated with the level of metals alleged to be present in Johnson's Baby Powder and Shower to Shower. To assume that a metal that has been shown to cause a particular type of cancer can cause other types of cancer (as several plaintiffs' experts claim) contradicts basic principles of toxicology and the Bradford-Hill guidelines as discussed above. It is thus inappropriate and scientifically unsound to make assumptions broadly and indiscriminately about a material's ability to cause ovarian cancer based on its potential association with other types of unrelated cancer that occur elsewhere in the body.

13.0 FRAGRANCE CHEMICALS

According to the materials reviewed in this case, Johnson's Baby Powder and Shower to Shower talcum powder products contain upwards of 130+ and 50+ fragrance chemicals, respectively (Int. 12/21/2017: #19). Fragrance compounds are added to many consumer products to improve the experience of their use. Some of the plaintiffs' experts claim that fragrance chemicals present in Johnson's Baby Powder and Shower to Shower are classified as carcinogens and/or act as irritants or sensitizers, thus inducing inflammatory responses that could lead to development of ovarian cancer (Plunkett 6/30/2021: p. 24; Carson 11/16/2018: p. 6; Crowley 11/12/2018: p. 12). However, a sufficient dose of an irritant must be received in order to elicit an inflammatory response by any chemical, which has not been shown to cause ovarian cancer at this time. Johnson's Baby Powder and Shower to Shower products are known to contain very low levels of fragrance (0.22% maximum content in Johnson's Baby Powder and 1% maximum content in Shower to Shower). Regardless of concentration, it is important to note that none of the fragrance components in either Johnson's Baby Powder or Shower to Shower has been reported to cause ovarian cancer in the scientific literature.

There are two major international bodies that monitor the safety of fragrances for consumer product use: the Research Institute for Fragrance Materials (RIFM) and the International Fragrance Association (IFRA). These organizations were established in 1966 (RIFM) and 1973 (IFRA) with similar goals that include evaluating fragrance safety, imparting that information with manufacturers and official agencies, and encouraging uniform safety standards, thereby promoting the safe use of fragrances and mixtures, and ultimately protecting the consumer. RIFM is a non-profit organization that conducts human health safety assessments of fragrance materials and publishes all data in peer-reviewed scientific journals. Carcinogenic and non-carcinogenic endpoints are evaluated for fragrances reviewed. The RIFM database now houses information for >6,000 materials, the largest database for fragrances in the world (RIFM, 2020, 2021). Importantly, the RIFM Expert Panel for Fragrance Safety is an independent body comprised of academic and adjunct scientists from around the world specializing in the fields of dermatology, pathology, toxicology, genetic toxicology, respiratory science, reproductive effects, epidemiology, and environmental science (EPFS, 2021). According to its Code of Practice, IFRA is also deeply committed to product safety. The first listed obligation is "IFRA members must ensure that the fragrance ingredients and mixtures they supply are safe for their intended uses and comply with applicable regulations and laws." (IFRA, 2021b).

Dr. Plunkett indicates that J&J documentation and its website "fail to provide specific information on the amount of each chemical component in the fragrance component of either Johnson's Baby Powder or Shower-To-Shower" (Plunkett 6/30/21: p. 23). However, she fails to recognize that the exact formulation is a matter of trade secret and this is standard practice for consumer product companies. In fact, she later includes an excerpt associated with diethyl phthalate that contradicts her own point:

> "Fragrances are usually composed of numerous individual substances that are blended together to achieve the desired scent. If a cosmetic product contains a fragrance, this is labelled using the word 'fragrance' or 'parfum' in the ingredients list rather than having to list out all of the individual

> components. This is legally allowed by the strict cosmetic safety laws and is common practice around the world. It is, however, not a way of 'hiding' ingredients as is sometimes, wrongly, claimed. All of the ingredients that make up the fragrance are still assessed very carefully as part of the overall product safety assessment. DEP and DMP may legally and safely be used as part of the fragrance mix. No substances banned from use as cosmetic ingredients are allowed to be used as components of cosmetic fragrances" (Plunkett 6/30/2021: p. 281).

As highlighted in the text from Dr. Plunkett's expert report, although fragrances may contain multiple individual chemicals, U.S. regulations allow fragrance ingredients to be listed on packaging simply as "Fragrance" to avoid revealing trade secret compositions (USFDA, 2020). To enhance transparency regarding ingredients in fragrances (including fragrances, stabilizers, malodorants, etc.), IFRA voluntarily provides information to regulators, customers and consumers through the creation of its IFRA Transparency List, which is a register of all fragrance ingredients used in consumer goods by the fragrance industry's customers across the globe (IFRA, 2021a). This list is compiled every five years through the utilization of an anonymous, confidential survey that collects fragrance ingredient information from IFRA members. RIFM has a collaborative relationship with IFRA; RIFM evaluates materials based on IFRA's Volume of Use Survey and has approved safety assessments for >85% of the single component fragrance materials currently in use. Thus, although these two organizations work extensively together, RIFM has not evaluated all fragrances and fragrance mixtures listed by IFRA.

Johnson's Baby Powder and Shower to Shower contain a combined 173 unique fragrance ingredients (Attorney's Eyes Only Exhibit 1 – Johnson's Baby Powder Fragrance Ingredients; Attorney's Eyes Only Exhibit 2 – Shower to Shower Fragrance Ingredients). Of these, RIFM has posted safety assessments for at least 161 (93%) on their database website (RIFM, 2024). This leaves 12 fragrances for which no RIFM review can be located. I have reviewed those chemicals to determine whether any has been associated with an increased risk for carcinogenicity in animals or humans. The results of my review are summarized in **Table 12** below.

Table 12: Assessment of Fragrance Chemicals in Johnson's Baby Powder and Shower to Shower on IFRA Transparency List Without RIFM Review History

CAS Number	Fragrance Chemical/Mixture	Evidence of Carcinogenicity/Basis from Mechanistic/ Epidemiology Studies	Carcinogenicity Classification
110-98-5	1,1'-oxybis-2-propanol	No evidence of carcinogenic activity in mice or rats of either sex up to 40,000 ppm in any organ including ovary[a]	N/A
3407-42-9	3-(5,5,6- trimethylbicyclo[2.2.1]hept-2-yl)cyclohexanol	No evidence of carcinogenicity in any organ	N/A
8050-07-5	Boswellia Carterii oil (frankencense)	No evidence of carcinogenicity in any organ (used as an anti-inflammatory agent with evidence for anti-carcinogenic effects)[b]	N/A
65113-99-7	3-methyl-5-(2,2,3- trimethylcyclopent-3-en-1- yl)pentan-2-ol	No evidence of carcinogenicity in any organ	N/A
4707-47-5	Benzoic acid, 2,4- dihydroxy-3,6-dimethyl-, methyl ester (veramoss)	No evidence of carcinogenicity in any organ	N/A
100-42-5	Ethenylbenzene (styrene)	See discussion in Styrene section below	IARC: 2A (Probably carcinogenic to humans) NTP: Reasonably anticipated to be human carcinogen
24111-17-9	Copper chlorophyll	No evidence of carcinogenicity in any organ	N/A

CAS Number	Fragrance Chemical/Mixture	Evidence of Carcinogenicity/Basis from Mechanistic/ Epidemiology Studies	Carcinogenicity Classification
133-37-9	Tartaric Acid	No evidence of carcinogenicity in any organ (GRAS food additive)	N/A
85507-69-3, 94349-62-9	Aloe Barbadensis leaf extract (aloe vera)	No human data was available for IARC review. Long term oral studies in rodents found association with GI cancers in rats and no cancers in mice.	IARC: 2B (Possibly carcinogenic to humans)
57-55-6	Propylene glycol	No evidence of carcinogenicity in any organ (animal studies indicate lack of carcinogenicity)[c]	N/A
70955-71-4	Indisan (sandela) reaction product	No evidence of carcinogenicity in any organ	N/A
1948-33-0	t-butyl hydroquinone	No evidence of carcinogenicity in any organ, including in ovary[d]	N/A

[a] NTP (2004) (Assessed as 43% of isomer mixture in dipropylene glycol, which contains 3 isomers)
[b] MSKCC (2021); Frank et al. (2009) ; Hostanska et al. (2002)
[c] USEPA (2006)
[d] NTP (1997)

Regarding the ingredients listed in **Table 12** for which there is no RIFM assessment available, the scientific literature and regulatory documentation do not suggest a causal relationship between exposure and ovarian cancer.

IFRA has published standards for a portion of the 161 fragrances that RIFM has assessed; for the majority, however, it has not issued a standard, likely because the RIFM review did not identify any health risks, including increased risk for cancer in the ovary (IFRA, 2021d). IFRA's list of published standards either prohibit or restrict the amount of a particular chemical or mixture in a product, and this information is based on findings of RIFM assessments. As of 2021, IFRA restriction standards with percent concentrations have been published for 35 of the fragrance components (IFRA, 2021c), although only 29 with assigned concentrations (e.g., several simply have a specification to add another ingredient when mixing) are currently in place. It is important to note that none of these ingredients are considered hazardous in the concentrations found in Johnson's Baby Powder or Shower to Shower, and none increases a woman's risk for ovarian cancer. Moreover, for many of these chemicals, the critical effect is phototoxicity. Additionally, when there is insufficient data for a safety assessment, IFRA prohibits use as a fragrance chemical. None of the ingredients in Johnson & Johnson's products has been prohibited by IFRA.

From the list of ingredients and CAS numbers in Johnson's Baby Powder and Shower to Shower products, the range of ingredient concentrations (%) used in the overall fragrance mixture, and the maximum percentage of combined fragrance ingredients in the finished product (0.22 or 1%, respectively), I calculated the highest possible minimum and maximum ingredient concentration (%) possible in the total finished product. I then compared the maximum ingredient concentration in the finished products to published IFRA restriction standards (where available) and calculated the difference between the IFRA standard and the concentration in the product. It is apparent that the concentrations of all ingredients in Johnson's Baby Powder and Shower to Shower for which an IFRA standard exists are well below the IFRA standard, and in many cases are multiple orders of magnitude lower. These results are presented in a table in **Appendix D**.

I have reviewed the scientific literature and government documents regarding a list of fragrance ingredients in Johnson's Baby Powder or Shower to Shower that Dr. Crowley highlights in his report as potentially causal in the development of ovarian cancer (Crowley 11/12/2018). My review of the scientific literature on these fragrances did not reveal a causal relationship between exposure and development of ovarian cancer, as discussed further below.

13.1 Fragrance Ingredients Highlighted by Dr. Crowley

In Dr. Crowley's expert report, he states that he "identified several chemicals in the fragrance mixture used by J&J in the talcum products with studies, in vitro and in vivo, published in peer reviewed journals demonstrating carcinogenicity, developmental or reproductive toxicity, genotoxicity, and or mutagenicity" (Crowley 11/12/2018: p. 12). However, Dr. Crowley testified in his deposition that he is

"not aware of an epidemiology study substantiating the causation of ovarian cancer from so-called fragrance chemicals" (Crowley 1/4/2019: p. 196). Summaries of the chemicals Dr. Crowley highlighted in his report follow.

13.1.1 Styrene

Styrene is primarily used and produced in industrial settings associated with development of synthetic materials. According to the National Center for Biotechnology Information, "[b]illions of pounds are produced each year to make products such as rubber, plastic, insulation, fiberglass, pipes, automobile parts, food containers, and carpet backing" (USNLM, 2021d). Styrene is also a component of combustion products such as those found in cigarette smoke and automobile exhaust (ATSDR, 2010). However, styrene is also produced naturally by plants, bacteria, and fungi, and is found in a variety of foods including fruits, vegetables, nuts, some beverages, and meats (ATSDR, 2010; USNLM, 2021d).

The majority of styrene exposure occurs in occupational settings involving manufacture of reinforced glass and styrene-butadiene rubber. For the general public, primary exposures are associated with cigarette smoking, although inhalation of ambient air and ingestion of styrene-containing foods are also sources of exposure. For non-occupational exposure in non-smokers, daily styrene intake is approximately 0.3-0.8 µg/kg body weight, the majority of which is inhaled from the environment (IARC, 1994). Carcinogenicity ratings developed by multiple agencies for styrene are included in **Table 13**.

Table 13: Carcinogenicity Ratings for Styrene

Agency	Rating
IARC	2A – Probably carcinogenic to humans
USEPA IRIS	Not evaluated
NTP	Reasonably anticipated to be a human carcinogen

The styrene carcinogenicity ratings for humans were largely based on limited evidence from epidemiological studies showing increased risk for leukemia and lymphoma in styrene workers, with IARC indicating in 2019 that there was no convincing or consistent evidence reported for any solid tumors in humans (IARC, 2019b; NTP, 2016). Cancer at other tissue sites has been reported in a few studies, although either too few cases were reported or other confounding exposures did not allow for establishment of a causal relationship (IARC, 2019b; NTP, 2008a).

Dr. Crowley states that "[s]tyrene has been recognized as a carcinogen by multiple governmental regulatory bodies" (Crowley 11/12/2018: p. 64), although the US government has not made this distinction. IARC and NTP have not indicated that styrene is a known human carcinogen, both choosing to assign a classification that indicates less confidence. Additionally, the USEPA has not yet developed a formal classification for styrene. Furthermore, NIOSH does not recognize styrene as a carcinogen, citing the following issues with the human and animal studies: "the human studies cannot be used to definitely demonstrate styrene's carcinogenicity because there were confounding exposures in these cohorts to

butadiene, a substance identified by the NTP as carcinogenic. The animal studies also have limitations, such as high background rates of cancer in the controls and non-treatment-related mortality in some of the test animals" (NIOSH, 2011, 2019). Similarly, OSHA does not recognize carcinogenicity as a chronic exposure hazard for styrene (OSHA, 2021).

Several epidemiology studies have examined ovarian cancer incidence among women occupationally exposed to styrene (Coggon et al., 1987; Ruder et al., 2014; Ruder & Bertke, 2017; Wong et al., 1994). However, low case numbers, inconsistent results, and potential for confounding exposures limit any conclusions to be made from these data. In rodent studies, long-term studies did not produce significant increases in ovarian tumors (Ponomarkov & Tomatis, 1978). Importantly, my review of the available scientific literature has not revealed any mechanistic, toxicologic, or epidemiologic data that suggests a causal relationship between styrene exposure and ovarian cancer in humans.

13.1.2 Para-Cresol

Para-cresol (p-cresol, also known as 4-methylphenol) is a member of the group of cresols, which are released into the environment during the burning of wood, coal, and fossil fuels, as well as from their manufacture (ATSDR, 2008). Many workers are exposed during manufacture of cresols, in chemical laboratories, in coal gasification and wood preserving facilities, and during application of paint, varnish, and insulation lacquers (ATSDR, 2008). The general public may be exposed via air (ambient air contains low levels of cresols from automobile exhaust, power plants, and oil refineries), in consumer products (cleaners, disinfectants), and in foods and beverages (USEPA, 2000). p-Cresol is primarily used in the fragrance and dye industries and to make antioxidants (ATSDR, 2008; USEPA, 2000b). Many foods and beverages contain low levels of cresols, including tomatoes, ketchup, asparagus, cheeses, butter, bacon, smoked foods, coffee, black tea, wine, and liquor (ATSDR, 2008).

The USEPA has evaluated cresols for potential carcinogenicity and has recommended a rating of "C – Possible human carcinogen" based on "only anecdotal information" in humans and increased incidence of dermal papillomas in mice (USEPA, 2000b). IARC and NTP have not yet evaluated p-cresol for carcinogenic potential in humans; however, the NTP concluded from a 2008 lifetime feed study in rodents that forestomach papillomas were associated with the highest dose cresol exposure (10,000 ppm, which also caused systemic toxicity as evidenced by weight loss), although exposure to all concentrations including 10,000 ppm in female rodents was not associated with malignancy in the ovary (NTP, 2008b). Ratings for p-cresol carcinogenic potential are included in **Table 14**.

Table 14: Carcinogenicity Ratings for para-Cresol (4-Methylphenol)

Agency	Rating
IARC	Not evaluated
USEPA IRIS	C – Possible human carcinogen

NTP	Not evaluated

Dr. Crowley indicates in his report that the USEPA considers p-cresol as "possibly carcinogenic" (Crowley 11/12/2018: p. 13), although it has not been established as a known human carcinogen. The USEPA cites two studies in mice in which p-cresol (at significantly higher concentrations than what may be included as a fragrance in Johnson's Baby Powder or Shower to Shower products) and known carcinogens were applied to mouse skin, which led to skin papillomas in some animals (USEPA, 1991a). Following application of dimethylbenzanthracene (DMBDA), one of the most powerful synthetic carcinogens available, 20% or 5.7% p-cresol (equating to 200,000 or 57,000 ppm) in benzene or acetone solvents were applied repeatedly over 12 or 20 weeks. Two additional studies were considered of limited value to the review panel. The USEPA concluded that "cresols can serve as tumor promoters of a polycyclic aromatic hydrocarbon" (USEPA, 1991a, p. 4). However, it is not clear what relevance these study results might have: (1) in a human, (2) in the ovary, (3) without the presence of a considerable amount of a polycyclic aromatic hydrocarbon or benzene present at the ovary, (4) with talc application, since the concentration of p-cresol (if present in talc) would be orders of magnitude lower than what was applied to mouse skin.

Importantly, animal and human studies have failed to establish a link between para-cresol exposure and ovarian cancer.

13.1.3 Coumarin

Coumarin is a natural chemical contained in the essential oils of many plants, including cinnamon, cassia, lavender and woodruff, and is used as a fragrance in a large number of personal care products (e.g., soaps, deodorants, perfumes) (IARC, 2000). Coumarin has been reported as present in concentrations up to 6% in perfumes (Rastogi et al., 1996 as cited by IARC, 2000). Coumarin is also found in tobacco, and is used in residential and industrial products to mask unpleasant odors and, as a flavoring agent for foods and beverages where it is reportedly permitted in concentrations of 10 mg/kg in food and 50 mg/kg in chewing gum (Lake, 1999 as cited by IARC, 2000). Coumarin has also been used to treat several medical conditions. For example, coumarins are commonly used as a treatment for several types of cancer, including prostate cancer, renal cell carcinoma, and leukemia, and are capable of mitigating radiation-induced side effects (Akkol et al., 2020). Additionally, coumarin derivatives have been shown to exhibit anti-carcinogenic properties against ovarian cancer cells (Nordin et al., 2016; Singh et al., 2011). IARC also cited ongoing clinical trials for anti-tumor potential for coumarin in the evaluation for cancers of the lung, breast, and kidney, as well as melanoma (IARC, 2000).

In addition to medicinal and other described uses, exposure to coumarin may occur from its production, its natural presence in many plants and essential oils, and industrial and consumer uses. Typical intake and recommended tolerable daily intake values for the general public are 0.06 mg/kg/day and 0.1 mg/kg/day, respectively. The typical intake includes approximately 0.02 mg/kg/day from dietary sources

and 0.04 mg/kg/day from cosmetic products, with study authors concluding that "exposure to coumarin from food and/or cosmetic products poses no health risk to humans" (Lake, 1999).

Due to a lack of carcinogenicity studies in humans, the IARC rating for coumarin was derived from experimental animal study results. IARC highlighted two studies in mice: in the first, oral coumarin administration led to increased lung tumors at the highest dose (200 mg/kg body weight for 103 weeks) in both sexes and increased incidence of hepatic tumors only in females at the low or medium dose (NTP, 1993 as cited by IARC, 2000). The second study in mice exposed to coumarin at concentrations up to 2,000 mg/kg diet failed to show a significantly elevated incidence of lung or other tumors in excess of the laboratory's historical control range (Carlton et al., 1996 as cited by IARC, 2000). As a result of these two studies in mice and another study in rats, which resulted in a low incidence of kidney cancer in males, IARC indicated that evidence regarding carcinogenicity was limited. Although coumarin is toxic in either hepatocytes or liver slices from rats, resistance to this toxicity is apparent in mice, rabbits and guinea pigs, monkey and human cells and/or liver slices, which, as IARC points out, is likely due to marked differences in the coumarin metabolic process between species (IARC, 2000). The NTP and USEPA have not evaluated coumarin's potential as a carcinogen (**Table 15**).

Table 15: Carcinogenicity Ratings for Coumarin

Agency	Rating
IARC	3 – Not classifiable as to its carcinogenicity in humans
USEPA IRIS	Not evaluated
NTP	Not evaluated

Dr. Crowley expresses concern in his report that coumarin had been identified by IARC as a "potential carcinogen" (Crowley 11/12/2018: p. 64). Similarly, Dr. Plunkett fails to recognize when referencing IARC's Group 3 Classification of coumarin that this rating does not imply that the chemical is carcinogenic in humans or even suspected to be a human carcinogen (Plunkett 6/30/2021: p. 24). The IARC Group 3 rating does not indicate that IARC believes that a substance is a potential carcinogen. Group 2B represents the status of "possibly carcinogenic to humans." According to the IARC preamble and as described previously in my report, Group 3 classification indicates that there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans in one or more tumor sites, there is not sufficient evidence in experimental animals in the remaining tumor sites, and data from studies in humans and mechanistic studies do not support another classification (IARC, 2019a). IARC also indicates that Group 3 classification often means that the agent is of unknown carcinogenic potential and evidence may suggest a lack of carcinogenicity. Thus, Dr. Crowley is incorrect to say that coumarin is a potential carcinogen, and his statement regarding "potential" carcinogenicity contradicts his earlier statement that "coumarin, eugenol, and d-limonene are "not classifiable" by IARC as to their carcinogenicity (Group 3)" (Crowley 11/12/2018: p. 21).

Importantly, my review of the scientific literature revealed no mechanistic or epidemiologic studies that reported an association between coumarin exposure and ovarian cancer.

13.1.4 Eugenol

Eugenol (principal extracted component of cloves) is an aromatic oil found in many edible, aromatic plants that is used to flavor foods and beverages (teas, alcohols), as an herbal treatment for toothache as well as gastrointestinal and respiratory complaints, and as an antiseptic and analgesic agent in dentistry (IARC, 1985; USNLM, 2021c). Among its primary uses, it is included in fragrances for its pungent clove scent. In essential oils, concentrations of eugenol may be as high as 90% (USNLM, 2021c). The USFDA considers clove oil, which contains 85-95% eugenol, as Generally Recognized as Safe for ingestion (USFDA, 2023). A study by the Flavor and Extract Manufacturers' Association of the United States estimated that the per-capita intake of eugenol is approximately 0.6 mg/day (IARC, 1985), although a much higher acceptable daily intake of 2.5 mg/kg body weight was established by the Joint FAO/WHO Expert Committee on Food Additives (WHO, 2005).

Because no studies were available to IARC that evaluated carcinogenicity of eugenol in humans, the IARC classification is based on data from animal studies, from which limited data existed to inform the rating. Results were equivocal for liver tumors in mice, and no increase in tumors was observed for rats (IARC, 1985, 1987).

Results from other testing were inconclusive due to inconsistency or inadequate study design. The NTP and USEPA have not evaluated the carcinogenic potential of eugenol for humans. In rodents, NTP determined that ingestion of up to 1.25% in the feed for 103 weeks did not lead to carcinogenicity in rats and results in studies with mice were equivocal for liver carcinogenesis (NTP, 1983). Eugenol carcinogenicity ratings are provided in **Table 16**.

Table 16: Carcinogenicity Ratings for Eugenol

Agency	Ratings
IARC	3 – Not classifiable as to its carcinogenicity in humans
USEPA IRIS	Not evaluated
NTP	Not evaluated

At low concentrations (as would be found in cosmetic talc), eugenol typically acts as an antioxidant and anti-inflammatory agent and is known to possess antigenotoxic activity (Jaganathan & Supriyanto, 2012). Eugenol has also been shown to inhibit cell migration and invasion in lung cancer cells, possibly by inhibiting lipid peroxidation, inflammation (via COX-2 gene), and reactive oxygen species generation (Fangjun & Zhijia, 2018).

Dr. Crowley indicates in his report that eugenol is a "potential carcinogen" (Crowley 11/12/2018: p. 64), although it has been assigned a Group 3 rating by IARC. Likewise, Dr. Plunkett also fails to acknowledge when referencing IARC's Group 3 Classification of eugenol that this rating does not imply that the chemical is carcinogenic in humans or even suspected to be a human carcinogen (Plunkett 6/30/2021: p. 24). As explained in my section on coumarin, a Group 3 rating does not equate to "potential carcinogenicity." Dr. Crowley contradicts his earlier statement that eugenol is "not classifiable" by IARC as to its carcinogenicity (Group 3)" (Crowley 11/12/2018: p. 21).

Importantly, my review of the scientific literature has revealed no evidence that eugenol exposure is associated with ovarian cancer development.

13.1.5 d-Limonene

d-Limonene is a common chemical in the atmosphere resulting naturally from vegetation (trees and shrubs), with 95% of citrus tree oil comprised of this chemical (IARC, 1993). Significant amounts of d-limonene are released into the environment from biogenic as well as anthropogenic sources (WHO, 1998). Although the majority of occupational exposure to d-limonene occurs during its synthesis and use as an industrial solvent, most exposure in the general public occurs through ingestion of food and certain drinks (e.g., ice cream and ices, sweets, baked goods, gelatins and puddings, and chewing gum non-alcoholic beverages) (IARC, 1993). d-Limonene is also included in dietary supplements and in many consumer products as a fragrance additive, such as perfumes and soaps (IARC, 1993; NCI, 2021). d-Limonene exposure in the general population can occur from any of the mentioned sources, or from indoor and outdoor air, from which a total daily intake of 0.3 mg/kg body weight has been estimated (IARC, 1999). According to the NCI, d-limonene exhibits chemopreventive, antineoplastic, and antitumor behavior, which NCI proposes may be due to activation of aldehyde dehydrogenase 3A1 (ALDH3A1), which decreases aldehyde level or inhibition of p21-dependent signaling and other mechanisms (NCI, 2021). IARC indicated in its 1999 report that when d-limonene was tested as a cancer-preventive agent in experimental models with known carcinogens, it "inhibited lung carcinogenesis in mice, preneoplastic stages of colon carcinogenesis in rats and pancreatic carcinogenesis in hamsters" (IARC, 1999).

NTP and USEPA have not evaluated d-limonene for human carcinogenicity. However, NTP performed a 2-year study in mice in which ingestion of up to 1,000 mg/kg body weight per day resulted in no clinical effects that were relevant to humans or related to administration of d-limonene (IARC, 1999; NTP, 1990; WHO, 1998b). d-limonene carcinogenicity ratings are included in **Table 17**.

Table 17. Carcinogenicity Rating for d-Limonene

Agency	Rating
IARC	3 – Not classifiable as to its carcinogenicity to humans
USEPA IRIS	Not evaluated
NTP	Not evaluated

The IARC carcinogen rating for d-limonene is based on experimental animal studies because no human studies were available for review. In addition to the NTP rodent studies previously mentioned, IARC reviewed an additional study (Kimura et al., 1996) that reported no treatment-induced tumors in rats. Additionally, three studies were reviewed and discussed by IARC that reported decreases in various types of tumors (lung, colon, pancreas), in rodents exposed orally or by intraperitoneal injection (El-Bayoumy et al., 1996; Kawamori et al., 1996; Nakaizumi et al., 1997 as cited by IARC, 1999). IARC explained that the only treatment-related carcinogenic effects have been in male rats, which metabolize d-Limonene and many other chemicals in a different way than humans, leading to nephrotoxicity (IARC, 1999).

As with coumarin and eugenol, Dr. Crowley's concluding statement that d-limonene is a "potential carcinogen" (Crowley 11/12/2018: p. 64) is incorrect, and he contradicts his earlier statement that d-limonene is "not classifiable" by IARC as to its carcinogenicity (Group 3)" (Crowley 11/12/2018: p. 21). Similarly, Dr. Plunkett fails to acknowledge when referencing IARC's Group 3 Classification of d-limonene that this rating does not imply that the chemical is carcinogenic in humans or even suspected to be a human carcinogen (Plunkett 6/30/2021: p. 24). This fragrance has been assigned an IARC group 3 rating which, in this case, is due to a rodent-specific carcinogenic response and no human data.

Importantly, my review of the scientific literature has yielded no studies showing an association between d-limonene exposure and ovarian cancer.

13.1.6 Benzophenone

Benzophenone is white solid with a flowery odor (USNLM, 2021b). Benzophenone is found naturally as a component of grapes at concentrations of 0.08–0.13 ppm (27 times higher level than when used as a flavoring agent or adjuvant), and in other foods and beverages such as papaya, black tea, and passion fruit (IARC, 2013; USFDA, 2018). Benzophenone is used extensively as a food additive: mean reported levels in the US range from 0.57 ppm in non-alcoholic beverages to 1.57 ppm in baked goods, and maximum reported levels range from 1.28 ppm in non-alcoholic beverages to 3.27 ppm in frozen dairy products (IARC, 2013). Benzophenone is also found in drinking water in small amounts, with an estimated intake of 0.52 to 17.6 µg per day (IARC, 2013).

Benzophenone is also used in perfumes, soaps, detergents, room deodorizers, and medications, such as antihistamines.

A derivative of benzophenone, benzenone-3, is added to sunscreens because it absorbs and scatters ultra-violet rays. Because of this and likely dietary ingestion, there is widespread exposure to benzophenone in the general population; CDC scientists have detected the sunscreen component (benzophenone-3) in the urine of nearly all people tested (CDC, 2017) and the Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) concluded that "there is no safety concern for benzophenone under the current condition of use as a flavouring substance" (Silano et al., 2017). A study by the Japanese Ministry of Environment found that benzophenone is a nearly ubiquitous component in the air as well, reporting detectable levels in 67/68 samples (The Japanese Ministry of Environment, 2006 as cited by IARC, 2013). The current workplace exposure limit (WEEL) for benzophenone in air established by the American Industrial Hygiene Association is 0.5 mg/m^3 for 8 hr TWA exposures (OARS, 2021).

In a lifetime benzophenone dietary study in rats and mice, the NTP reported that no carcinogenic effects were observed in the ovary with up to 312 ppm benzophenone in feed (NTP, 2006). Benzophenone exposure resulted in one ovarian histiocytic sarcoma in a female rat, although there was no apparent dose-dependent relationship since no animals in the low and high dose group developed this tumor. In mice, which are more sensitive to histocytic sarcomas than rats, 1/50 in the 625 ppm group and 2/50 in the 1,250 ppm group developed ovarian histiocytic sarcomas. These results for the ovary were likely not significant (statistical evaluation for ovarian histiocytic sarcoma not provided). NTP combined all histiocytic sarcomas into one group, which also included histiocytic sarcomas of many other organs (e.g., liver, lung, gastrointestinal tract, heart, thyroid, mammary gland) and found that all neoplasms falling into that one category were significant at the mid-dose (625 ppm) only. NTP concluded that:

> "There was equivocal evidence of carcinogenic activity of benzophenone in female F344/N rats based on the marginally increased incidences of mononuclear cell leukemia and histiocytic sarcoma. There was some evidence of carcinogenic activity of benzophenone in male B6C3F1 mice based on increased incidences of hepatocellular neoplasms, primarily adenoma. There was some evidence of carcinogenic activity of benzophenone in female B6C3F1 mice" (NTP, 2006, p. 56).

NTP also reported that benzophenone was not mutagenic or genotoxic *in vitro* or *in vivo*. It is also noteworthy that the control animals exhibited higher incidence of inflammation that the treatment animals.

Dermal application of up to 50% benzophenone in acetone twice a week for 120 weeks did not produce a carcinogenic response in the skin of mice (Stenback & Shubik, 1974 as cited by IARC, 2013).

In 2017, the European Food Safety Agency Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) reviewed the tolerable daily intake of 0.03 mg/kg body weight per day established by the CEF panel in 2009, finding that the "conservative" value was still appropriate to cover all non-

neoplastic effects in the chronic toxicity studies and the neoplastic effects reported in the rodent carcinogenicity studies (Silano et al., 2017, p. 13).

In a review of benzophenone, IARC concluded that there is "sufficient evidence of carcinogenicity in experimental animals;" however, IARC classified benzophenone as "possibly carcinogenic to humans" (Group 2B) because no human data are available for evaluation showing an association (or lack thereof) between benzophenone and ovarian cancer (IARC, 2013, p. 301). The USEPA and NTP have not reviewed benzophenone for human carcinogenicity (**Table 18**).

Table 18: Carcinogenicity Rating for Benzophenone

Agency	Rating
IARC	2B – Possibly carcinogenic to humans
USEPA IRIS	Not evaluated
NTP	Not evaluated

In his report, Dr. Crowley states that "[b]enzophenone was recently removed from use in foods by FDA due to histiocytic sarcoma observed in ovaries and uterus, higher incidences of kidney tumors and leukemia in animal studies, and in vivo estrogenic activity." (Crowley 11/12/2018: p. 48). However, as explained above, Dr. Crowley is clearly misinterpreting the results of the NTP animal study. Specifically, in the final ruling, the FDA never mentions ovarian or uterine cancer; nor does the FDA include any wording regarding estrogenic properties (USFDA, 2018). Thus, his statement is false and misleading. Dr. Crowley also indicates that benzophenone has no IFRA Standard (Crowley 11/12/2018: p. 64); however, an IFRA Standard is not required and would indicate that benzophenone is neither restricted nor prohibited for use as a fragrance.

13.1.7 Musk Ketone

Musk ketone is a crystalline solid used as a fragrance ingredient in cosmetics, colognes, shampoos, toiletries, detergents, fabric softeners, household cleaning products, and other fragrance-containing products (EC, 2005). The EU Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) estimated that dermal exposure resulting from use of these products is approximately 200 µg/kg/day in adults.

There are no carcinogenicity data for musk ketone; however, similar compounds have been tested and evaluated for carcinogenic potential. According to the Scientific Committee on Health And Environmental Risks (SCHER), musk xylene has been classified as a "category 3 carcinogen," based on an 80-week oral carcinogenicity study in mice and absence of genotoxicity (EC, 2006). According to the report, "the classification of musk xylene as "category 3 carcinogen" is considered as a borderline case since an

increase in liver tumours in the highly sensitive B6C3F1 mouse is considered of little relevance for human hazard assessment " (EC, 2006, p. 3) The committee reasoned that since musk ketone possesses similar physicochemical properties and similar liver enzyme induction capability as musk xylene, musk ketone should also be assigned a Category 3 rating (insufficient information from animals studies and the available information is otherwise not adequate for making a satisfactory assessment) (EC, 2005, p. 27). The ECHA has concluded that "[t]here is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already." (EC, 2005, p. 27).

Table 19: Carcinogenicity Rating for Musk Ketone

Agency	Rating
IARC	Not evaluated
USEPA IRIS	Not evaluated
NTP	Not evaluated
SCHER	Category 3 – inadequate information

Importantly, my review of the scientific literature has yielded no studies showing an association between musk ketone exposure and ovarian cancer.

13.1.8 Irritants, Sensitizers, and Allergens

A review of available toxicology databases including the National Library of Medicine's TOXNET database, Cosmetic Ingredient Review (CIR) compendium, and the IFRA standards library, indicates that some of the fragrance chemicals present in Johnson's Baby Powder and Shower to Shower demonstrate potential as irritants, sensitizers, and/or allergens. These results are often obtained from animal studies or human patch testing with the neat (100%) chemical or formulations at concentrations greater than 1% (HSDB, 2020)

According to the Global Harmonized System (GHS), in conjunction with the OSHA Hazard Communication Standard, the concentration of ingredients present in a mixture, such as Johnson's Baby Powder and Shower or Shower, indicates whether the mixture itself is classified as a skin irritant or hazardous to the skin (United Nations, 2023). The fragrance chemicals present in these products make up an extremely low percentage (<0.2%) of the total products. Per GHS guidelines, none of the fragrance compounds reach concentrations that would cause Johnson's Baby Powder to be classified as an irritant, or as corrosive or sensitizing, regardless of the classification of any single additive during its manufacture. Any consideration of the potential hazards associated with the fragrance chemicals present in Johnson's Baby Powder or Shower to Shower needs to consider dose in the context of any claims of irritation and inflammatory response. Dr. Crowley testified in his deposition that he did not review the GHS hazard codes for the fragrances; he only reviewed the Safety Data Sheets (Crowley 1/4/2019: p. 303-05). This indicates that he reviewed each of these substances at either full concentration or in a concentrated form, which is not

standard risk assessment protocol for evaluation of hazards associated with mixtures, in which the chemical of interest is diluted.

Evaluation of the irritation potential for the entire mixture is the correct approach, rather than for each individual component, which will ultimately be included as a very low percentage of the mixture (0.22% of Johnson's Baby Powder and ≤1% in Shower to Shower for all fragrances combined). If all fragrance ingredients included in Johnson's Baby Powder and Shower to Shower were considered irritants and by the same mechanism (e.g., all are highly acidic), then an additive approach might be used to determine the overall irritancy potential of the fragrance-containing powders. However, the mixture of fragrance chemicals in these products is diverse in composition and many do not cause any irritation at full strength. Thus, an additive approach should not be used to estimate overall irritation potential of the fragrances. For the sake of conservatism, if we assumed that all fragrances included in these products were severe irritants at full strength and had a similar mechanism of action, the GHS Classification Criteria could be used to classify the irritancy of mixture using the additive approach. The total mixture is not considered an irritant if the concentration of the irritant components (fragrances in this case) is less than 1%. To evaluate mixtures for which an additive approach does not apply, concentrations of ingredients must also be at least 1% of the overall mixture in order to be classified as hazardous (see table below). This GHS approach is considered mandatory protocol for evaluating ocular and dermal irritancy of mixtures by OSHA (OSHA, 1910.1200 App A). The USEPA has also recommended this approach for other consumer products as an alternative to animal testing of mixtures (USEPA, 2021b).

Table 20: GHS Classification Criteria for Mixtures

Ingredient	Concentration	Mixture Classified as: Eye
Acid with pH ≤ 2	≥1%	Category 1
Base with pH ≥ 11.5	≥1%	Category 1
Other corrosive (Category 1) ingredients for which additivity does not apply	≥1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥3%	Category 2

Source: Table A.3.4—Concentration of Ingredients of a Mixture for Which the Additivity Approach Does Not Apply, That Would Trigger Classification of the Mixture as Hazardous to the Eye
https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1200AppA

Thus, given the concentrations of fragrance in Johnson's Baby Powder and Shower to Shower products and even assuming a worst-case scenario in which all fragrances were severe mucosal irritants (they are not), one could not consider the fragrance mixture at the concentration it is formulated in either product to be irritating.

13.1.9 Summary

Based on my review of the fragrances that are formulated into Johnson's Baby Powder and Shower to Shower, it is clear that none of these components is known to be associated with ovarian cancer. Moreover, to disregard dose and assume that any concentration is capable of causing irritation and inflammation to a degree that is allegedly sufficient to elicit cancer clearly misinterprets the mechanisms involved in developing and sustaining cells that lead to a cancerous tumor (see previous discussion on carcinogenesis).

Often, hundreds of fragrances are present in single cosmetic or other consumer products, which have been deemed by regulatory organizations to be safe because the levels of these fragrances are included in extremely low concentrations that do not elicit irritation or inflammation. Chlorine is one of the most irritating chemicals known to man (when concentrated), but we add it to our drinking and bathing water intentionally because it is beneficial in low concentrations without causing irritation. Low concentrations of many chemicals, like those present in the products under consideration (see **Appendix D** for fragrance concentrations), are used in products everywhere safely. It is important to note that none of the fragrances in the Johnson's Baby Powder or Shower to Shower is present in these products at concentrations that would cause concern from a health or regulatory standpoint. Plaintiffs' experts, including Dr. Crowley, have purposefully ignored this critical detail of dose and the required threshold for irritation or other adverse health effects, which is scientifically unsound.

13.2 Responses to Plaintiffs' Experts Comments Regarding Fragrance Ingredients and Dose

Dr. Plunkett consistently ignores the critical concept of dose and the fact that many chemicals we use in our daily routines can be toxic at a full strength. Fragrances are not present in talcum powder products at 100% concentration or even at concentrations that may be tested in animals. As I have demonstrated in **Appendix D**, concentrations of individual fragrances present in Johnson's Baby Powder and Shower to Shower are many times less than concentrations that could pose any health hazard. The same concept is applicable to pharmaceuticals: a drug approved by the FDA is considered safe at the concentration at which the ingredient is included in the formulated product (e.g., tablet, pill) but may cause unintended effects at higher concentrations (e.g., analgesics, anticoagulants, blood pressure medications). As discussed earlier, even if every individual fragrance present in Johnson's Baby Powder and/or Shower to Shower were determined to be a severe irritant at full strength, which is not the case, and even if each fragrance were irritating for a similar reason (e.g., all were at high pH), which is also not the case, the

combination of all fragrances together would not be irritating because both the individual fragrances (< 0.05%) and the total fragrance mixture (≤ 1%) are formulated into the final product at such low concentrations.

Dr. Plunkett includes detailed toxicity information about the fragrances in Appendix D of her report, highlighting the fact that IFRA has set limits for some of the fragrances. The fact that IFRA and RIFM have evaluated these fragrances should create a sense of security because the fragrances have distinct limits to prevent excess exposure associated with potential health hazards. Dr. Plunkett also refers to the irritating properties of some fragrances and states that "consumers have never been provided with information that any of the ingredients in the Johnson & Johnson fragrance posed a potential human health risk" (Plunkett 6/30/2021: p. 24). This statement is misleading, because the fragrances contained in the talcum powders are present at concentrations that do not pose a risk of irritancy, or any other health risk. For Dr. Plunkett to suggest otherwise contradicts fundamental toxicological principles of dose and reflects unsound science. As previously described, a table of select fragrance ingredients in Johnson's Baby Powder and Shower to Shower is included in **Appendix D** of my report showing that the fragrance chemicals are present at concentrations that are far lower, often multiple orders of magnitude lower, than IFRA standards.

Dr. Crowley similarly ignores dose, the most fundamental aspect of toxicology risk assessment. Dr. Crowley states that "[s]everal fragrance chemicals are irritants, sensitizers and allergens that can cause inflammation and oxidative stress" (Crowley 11/12/2018: p. 64). Dr. Crowley also includes a list of fragrance ingredients that he alleges cause irritation (Crowley 11/12/2018: Appendix A, Appendix B). However, as stated earlier, nearly all chemicals induce some form of adverse cellular response, such as irritation, at sufficiently high concentrations. For many of the fragrance ingredients listed, Dr. Crowley briefly presents toxicology data for the ingredient tested both neat (100%) and at lower or diluted concentrations; the latter of which is still many times higher than any concentration present in Johnson's Baby Powder or Shower to Shower. These studies show that a clear dose-response relationship is identified for these ingredients, such that the lower concentration either had no effect or a significantly milder response.

Using one such example, the excerpt Dr. Crowley provides for benzyl benzoate states that "Benzyl benzoate is a primary skin irritant (Schwartz, Tulipan & Birmingham, 1957), but used as a 20% emulsion in the treatment of scabies in 1,000 persons it produced no dermatitis (Graham 1943)" (Crowley 11/12/2018: p. 103). Similarly, the toxicity information that Dr. Crowley includes for methyl isoeugenol states that "Methyl isoeugenol applied full strength to intact on abraded rabbit skin for 24 hr under occlusion was irritating (Keating, 1972). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972)" (Crowley 11/12/2018: p. 72). For many of the fragrances that Dr. Crowley lists, data were only collected following testing of a neat (100%) solution, which is not relevant when evaluating potential hazards associated with exposure to a mixture that

contains the ingredient at substantially lower concentrations, such as the concentrations present in talcum powders. The fact that Dr. Crowley is unable to interpret these data showing a dose-dependent requirement for effects supports his testimony that he does not consider himself an expert in toxicology (Crowley 1/4/2019: p. 30).

Dr. Crowley continues to disregard the concept of dose in one of his concluding statements, stating that "[i]n vitro and in vivo studies have demonstrated that several fragrance chemicals have biological activity, including reproductive and developmental effects. These studies have been published in peer reviewed scientific journals" (Crowley 11/16/2018: p. 64). This may be true for certain chemicals at much higher concentrations than are included in cosmetic products. However, there is no evidence to suggest that all reproductive/developmental toxicants are also ovarian carcinogens. Further, I have not found any evidence to suggest that the fragrance ingredients present in Johnson's Baby Powder or Shower to Shower are ovarian carcinogens. It is not uncommon for chemicals to cause reproductive or developmental effects only at high exposure levels that are acutely toxic to the mother (e.g., maternal toxicity), but these chemicals would not be considered developmental toxicants or teratogenic agents (Paumgartten, 2010). In fact, the USEPA stated that "[a]t doses that cause excessive maternal toxicity (that is, significantly greater than the minimal toxic level), information on developmental effects may be difficult to interpret and of limited value" (USEPA, 1991b)

Dr. Crowley testified that he did not perform a risk assessment or risk characterization to arrive at his conclusions (Crowley 1/4/2019: p. 123, 125). He continued that a risk assessment was not necessary and indicated that "I relied upon the available information for the chemicals from, you know, MSDS sheets and the published studies that did do those things" (Crowley 1/4/2019: p. 131-133, 134-135). However, the MSDSs (Material Safety Data Sheets) for fragrance ingredients contained in Johnson's Baby Powder or Shower to Shower products do not include ovarian cancer as a potential effect of exposure, and MSDS documents do not typically consider dose when describing the potential hazards associated with the substance. Often, hazard statements found in the MSDS are based on results from studies in which the substance was tested at 100% or high concentrations compared to what is present in Johnson's Baby Powder or Shower to Shower products, and possibly by a different exposure route. Furthermore, published studies on any of the fragrance chemicals are unlikely to be performed at such extremely low concentrations (< 1%). Thus, information from either of the two general sources that Dr. Crowley cites requires evaluation by a toxicologist to understand the dose-response implications of the described effects.

Dr. Crowley further alleged that only one molecule of a genotoxic substance was required to increase risk (Crowley 1/4/2019: p. 125); however, he later stated that he does not believe that fragrance chemicals are capable of genotoxic response (Crowley 1/4/2019: p. 126).

Additionally, an important part of risk assessment involves consideration of whether the substance is capable of causing the effect of interest at any dose. Thus, even if fragrance chemicals contained in talc were to reach the ovary and cause inflammation (in low or high concentrations, and for short or long durations), it has not been established that this supposed inflammation resulting from such an exposure from fragrance chemicals, or talcum powder in general, has led to ovarian cancer. Dr. Crowley is not a toxicologist and stated that he never performed any independent research with respect to fragrance chemicals, inflammation or cancer (Crowley 1/4/2019: p. 67, 77). Therefore, it is not surprising that he is unaware of recent developments in the areas of the dose-dependent threshold methodology and genotoxic risk assessment. It is also not surprising that he would fail to understand that an established cause-effect relationship at any dose is standard practice associated with performing a risk assessment, which is used to then establish or disprove a potential causal relationship.

Finally, Dr. Crowley testified at his deposition that he was not asked to consider "level of exposure" (dose) and did not make any effort to "discern whether any individual plaintiff was actually exposed to harmful levels of fragrance chemicals" (Crowley 1/4/2019, pp. 107-108). Dr. Crowley further testified that he was not given the necessary information to determine the concentration of each chemical (Crowley 1/4/2019, p. 124). However, the maximum concentration of fragrance in the Johnson's Baby Powder and Shower to Shower products can be determined by adding the maximum amount (on a percentage basis) for each ingredient included on the provided fragrance ingredient lists. Thus, it is not true that Dr. Crowley could not estimate the amount of fragrance in the cosmetic talc products in order to consider the effect of dose in his assessment.

14.0 CONCLUDING OPINION

For the reasons stated above, it is my opinion, to a reasonable degree of scientific certainty, that there is insufficient evidence in the scientific literature to support the conclusion that cosmetic talc causes or contributes to the development of ovarian cancer. It is my further opinion that plaintiffs' experts' causation opinions are critically flawed and contrary to fundamental principles of toxicology and epidemiology. In addition, there is no evidence that the potential presence of other constituents (e.g. asbestos, fibrous talc, heavy metals, or fragrance ingredients) in talcum powder poses a risk for ovarian cancer to talcum powder users.

Respectfully,

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Appendix A

Curriculum Vitae of Paul Nony, PhD, CIH, CSP

CTEH®

Paul Nony, Ph.D., CIH, CSP

Senior Vice President, Principal Toxicologist

CONTACT

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EDUCATION

Ph.D., Interdisciplinary Toxicology, 2001
University of Arkansas for Medical Sciences, Little Rock, AR

B.A., Biology,
Hendrix College, Conway, AR 1996

Professional Licenses, Certifications and Accreditations:
Certified Industrial Hygienist #11135CP
Certified Safety Professional #33934
Society of Toxicology, Full Member
American Industrial Hygiene Association
South Central Chapter Society of Toxicology
American Conference of Governmental Industrial Hygienists

INTRODUCTION

Dr. Paul Nony is Senior Vice President and Principal Toxicologist and has over twenty years training and professional experience in the fields of chemical emergency response, human and environmental toxicology and risk assessment, cell biology, physiology, and cancer research. He received his Ph.D. in Interdisciplinary Toxicology from the University of Arkansas for Medical Sciences (UAMS) and spent two years in a postdoctoral fellowship at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, NC. Upon completion of his fellowship in 2003, Dr. Nony accepted a position as a Toxicologist at CTEH® in Little Rock, AR. Dr. Nony is a board Certified Industrial Hygienist (CIH) through the American Board of Industrial Hygiene, a board Certified Safety Professional (CSP) through the Board of Certified Safety Professionals, and a member of the American Industrial Hygiene Association, the American Conference of Governmental Industrial Hygienists, and the Society of Toxicology.

Dr. Nony participates in a variety of projects with scopes ranging from chemical product evaluation to emergency response to environmental contamination to evaluating the chemical causes of human disease. He is consulted by clients for his expertise in worker chemical exposure incidents and is asked to convey toxicological information to workers, supervisors, and health care providers alike to improve the communication of health risks to workers and employers and the quality of toxicological information used by treating physicians. He also is called by government agencies as well as hazardous materials shipping, handling, and manufacturing and petroleum industry clients to provide expert toxicological and human health risk support in emergency situations where releases of hazardous materials pose a threat to workers, residents, and the environment. Dr. Nony possesses experience and expertise in industrial hygiene, risk assessment, and the human toxicology of many classes of chemicals that may pose a risk to human health through the contamination of air, water, and/or soil. He also has expertise in emergency preparedness and planning and is a trusted partner of industry and governments alike in emergency response management and safety.

RELEVANT EXPERIENCE

Postdoctoral fellow at the National Institute for Environmental Health Sciences, Metastasis Division, Laboratory of Molecuar Carcinogenesis, Research Triangle Park, NC

Investigated effects of environmental chemicals on the adhesive properties of human breast cancer cells.

Performed immunochemical analyses and polymerase chain reactions to identify proteins and signaling pathway activation in tumor cells.

Predoctoral Researcher, Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR

Isolated primary kidney cell cultures from rabbits and examined repair and regeneration responses following toxic chemical exposures

Performed cell cycle analyses using flow cytometry and confocal microscopy.

Mentored graduate and undergraduate students.

Predoctoral Researcher, Division of Neurotoxicology, USFDA, National Center for Toxicological Research, Jefferson, AR

Studied the effects of neurotoxicants on metabolic enzymes in rodent brain tissue.

Safety/emergency management and crisis preparedness experience

- **Mastered immunohistochemical and cytological methods.**
- **Tabletop and functional drills and exercises**
- **Type I Incident Safety Officer Experience**
- **NIMS/ICS 100, 200, 300, 400, 700, 800, SOFR**
- **CA Spill Management Team Certified**

PUBLICATIONS

Peer-Reviewed Publications:

1. Scribner, K., Nony, P. A., Kind, J., Still, K. R. and Hesterberg, T. (2019) 'Chapter 27 — Toxicology of Asbestos', in Luttrell, W.E., Still, K.R., Church, J.A. & Beyer, L.A. (eds.) Toxicology Principles for the Industrial Hygienist. Falls Church, VA: AIHA, pp. 398-411.
2. Wnek, S. M., Kuhlman, C. L., Harrill, J. A., Nony, P. A., Millner, G. C. and Kind, J. A. (2018) 'Chapter 5 - Forensic Aspects of Airborne Constituents Following Releases of Crude Oil Into the Environment A2 - Stout, Scott A', in Wang, Z. (ed.) Oil Spill Environmental Forensics Case Studies: Butterworth-Heinemann, pp. 87-115.
3. Harrill J.A., Wnek, S.W., Pandey R.B., Cawthon, D., Nony, P.A., Goad, P.T. (2014) Strategies for Assessing Human Health Impacts of Crude Oil Releases. International Oil Spill Conference Proceedings. 4. Nony, P., Scribner, K., Hesterberg, T., (2014) Synthetic Vitreous Fibers. In: Wexler, P. (Ed.), Encyclopedia of Toxicology, 3rd edition vol
4. Elsevier Inc., Academic Press, pp. 448–453.
5. G.C. Millner and P.A. Nony (2010) No Time to Lose: Preparation, Quick Thinking are Essential for Emergency Response and Analysis. The Synergist. June/July 0607/10.
6. Nony, P. A. (2008) Clearing the Air. Risk Management. Aug; 55(8):59.
7. Nony PA, Nye, AC, Sandau, CD. (2006). PCB data validation and interpretation for establishing fish consumption guidelines in the USA – A Texas case study. Organohalogen Compounds. 68; 2214-2217.
8. Laura L. Ferriby, Jeffrey S. Knutsen, Mark Harris, Paul Nony, Kenneth M. Unice, Dennis Paustenbach and Paul Scott (2006). Evaluation of PCDD/F and Dioxin-like PCB Serum Concentration Data from the 2001-2002 National Health and Nutrition Examination Survey of the United States Population. J Exp Sci Environ Epidemiol. 1-14.
9. P.A. Nony, S.B. Kennett, W.C. Glasgow, K. Olden, and J.D. Roberts (2005). 15(S)-Lipoxygenase-2 Mediates Arachidonic Acid-stimulated Adhesion of Human Breast Carcinoma Cells through the Activation of TAK1, MKK6, and p38 MAPK. J Biol Chem. 280 (36), 31413- 31419, 2005.
10. P.A. Nony and R.G. Schnellmann (2003). Mechanisms of renal cell repair and regeneration after acute renal failure. J. Pharmacol. Exp. Ther. 304: 1-8.
11. P.A. Nony and R.G. Schnellmann (2001). Role of collagen IV and collagen-binding integrins in renal cell repair following toxicant injury. Mol. Pharm. 60: 1226-1234.
12. P.A. Nony, G. Nowak, and R.G. Schnellmann (2001). Collagen IV promotes the repair of renal cell functions following sublethal toxicant injury. Am. J. Physiol. Ren Physiol. 281:F443-F453.
13. P.A. Nony, J.D. Roberts, W.C. Glasgow, and K. Olden (2002). "15-Lipoxygenase-2 mediates arachidonic acidstimulated adhesion of human breast carcinoma cells to type IV collagen". Clin Exper Metastasis (19, S1): 63, S-14.
14. P.A. Nony and R.G. Schnellmann (2001). Role of collagen IV and collagen-binding integrins in renal cell repair following sublethal toxicant injury. The Toxicologist, 60(1): 308, #1464.
15. P.A. Nony, G. Nowak, and R.G. Schnellmann (2000). Ascorbic acid-stimulated deposition of collagen IV is associated with repair of renal cell functions following sublethal injury. The Toxicologist, 54(1): 400, #1878.
16. Scallet, A.C., Nony, P.A., Rountree, R.L., and Binienda, Z.K. (2001). Biomarkers of 3-nitropropionic (3-NPA)- induced mitochondrial dysfunction as indicators of neuroprotection. Ann. N. Y. Acad. Sci. 939: 381-392.
17. P. A. Nony, G. Nowak, and R.G. Schnellmann (1999). Disruption of collagen type IV synthesis in renal proximal tubular cells by the nephrotoxicant dichlorovinyl-Lcysteine. FASEB Journal, 13(5, Part 1): A341 (263.6).
18. Nony, P.A., Scallet, A.C., Rountree, R., Ye, X., and Binienda, Z. (1999). 3-Nitropropionic acid (3-NPA) produces hypothermia and inhibits histochemical labeling of succinate dehydrogenase (SDH) in rat brain. Metabolic Brain Disease, 14(2): 83-94.
19. Nony, P.A., Scallet, A.C., Rountree, R., Ye, X., and Binienda, Z. (1997). 3-Nitropropionic acid (3-NPA) produces hypothermia and inhibits histochemical labeling of succinate dehydrogenase (SDH) in rat brain. 27th Annual Meeting; Society for Neuroscience Abstracts, 23(Part 2): 855.5.

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Senior Vice President, Principal Toxicologist

20. Scallet, A.C., Ye, X., Rountree, R., Nony, P.A., and Ali, S.F. (1996). Ibogaine produces neurodegeneration in rat, but not mouse, cerebellum: Neurohistological biomarkers of Purkinje cell loss. Ann. New York Acad. Sci., 801:217-26.

Abstracts:

1. P. Nony, N. Mabile, J.T. Wilson (2018). "Controlled In-Situ Burn of Crude Oil in Extreme Cold Weather Conditions." Abstract presented at the 2nd Annual Clean Waterways Inland River Response Conference, St. Louis, MO.
2. P. Nony (2018). "Preparing for and Responding to Posthurricane Chemical and Biological Threats to Public Health and the Environment." Abstract presented at the 39th Annual Meeting of the American College of Toxicology, West Palm Beach, FL.
3. K. Tuttle and P. Nony (2017). "Vapor Intrusion and Chlorinated Solvents in Commercial and Industrial Settings." Abstract presented at the Alliance for Hazardous Materials Professionals 2017 National Conference, Fort Worth, TX.
4. P. Nony (2017). "Personal Protective Equipment (PPE) for Responders and the Public." Abstract presented at the 2017 Clean Gulf Conference, Houston, Texas.
5. Harrill, J. A.; Wnek, S. M.; Cawthon, D. R.; Nony, P. A., and Kind, J. A. Derivation and Comparison of Occupational Exposure Limits (OELs) for Hydrocarbon Vapor Mixtures Emitted from Bakken and Non-Bakken Crude Oil. The Toxicologist. 2015; 144(1):38-39.
6. Thomas Hesterberg, Paul Nony, Kelly Scribner, Michael Berg, Paul Watson, 2014. Potential Exposure Threshold of Chrysotile Asbestos. Poster presented at the 53rd Annual Society of Toxicology Meeting and Tox Expo, Phoenix, AZ.
7. Davis, C.; Kind, J.; Shelnutt, S.; Nony, P., and Millner, G. (2011) Effective Monitoring and Protection of Workers and the Community during Waterway Chemical Spills. In. 21st Annual Clean Gulf Conference, San Antonio, TX.
8. Davis, C.; Kind, J.; Shelnutt, S.; Nony, P., and Millner, G. (2011) "Effective Monitoring and Protection of Workers and the Community during Waterway Chemical Spills." In. 2011 International Oil Spill Conference Proceedings; Portland, OR. Washington, DC: American Petroleum Institute.
9. Cox, R.D. and Nony, P.A. (2010) "A Quantitative Method for Polychlorinated Dioxin/Furan Congener Source Comparisons." Abstract presented at Dioxin 2010 in San Antonio, TX.
10. Cox, R.D., Nony, P.A., and Liles, C.H. (2010) "Summary of Mortality Due to Diabetes and Diabetes-Related Conditions in Human PCB Cohort Studies." Abstract presented at Dioxin 2010 in San Antonio, TX.
11. P. Nony, D. W. Gaylor, G. C. Millner, A. C. Nye and J. Gandy (2008). "Residual PAHs, PCBs, PCDDs, and PCDFs in Soil and House Dust Following an Industrial Chemical Release and Fire." Abstract presented at the 47th Annual Meeting of the Society of Toxicology in Seattle, WA.
12. J. Kind, P. Nony, and D. Hewitt (2008). "The Protective Effect of the Upper Airways Against Water Soluble Irritant Gas Exposure – A Case Study of Acute Ammonia Exposure." Abstract presented at the 47th Annual Meeting of the Society of Toxicology in Seattle, WA.
13. Courtney D. Sandau and Paul A. Nony (2006). "Quality Assurance-Quality Control (QA-QC) Requirements and Statistical Interpretation of PCBs in Fish and Sediment Samples for Litigation Involving Environmental Forensics. " Abstract presented at Environmental Forensics: Chemical, Physical, and Biological Methods Conference, University of Durham, United Kingdom.
14. Nony PA, Nye, AC, Sandau, CD (2006). "PCB Data Validation and Interpretation For Establishing Fish Consumption Guidelines In The USA - A Texas Case Study." Abstract presented at the 26th International Symposium on Halogenated Persistent Organic Pollutants (Dioxin 2006), Oslo, Norway. 15.Laura L. Ferriby, Jeffrey S. Knutsen, Mark Harris, Paul Nony, Kenneth M. Unice, Dennis Paustenbach and Paul Scott (2006). "Evaluation of PCDD/F and Dioxin-like PCB Serum Concentration Data from the 2001-2002 National Health and Nutrition Examination Survey of United States Citizens." Abstract presented at the 45th Annual Meeting of the Society of Toxicology, San Diego, CA.

Presentations:

1. P. Nony, N. Mabile, J.T. Wilson (2018). "Controlled In-Situ Burn of Crude Oil in Extreme Cold Weather Conditions." Platform talk at the 2nd Annual Clean Waterways Inland River Response Conference, St. Louis, MO.
2. P. Nony (2018). "Preparing for and Responding to Posthurricane Chemical and Biological Threats to Public Health and the Environment." Platform talk presented at the 39th Annual Meeting of the American College of Toxicology, West Palm Beach, FL.
3. P. Nony (2018). "Exposure Management: First Responder Fire Smoke Exposures." Platform talk presented at the Williams Fire & Hazard Control Xtreme Industrial Fire & Hazard Training, College Station, TX.
4. Nony, P. (2017) "Personal Protective Equipment (PPE) for Responders and the Public." Presented at the 27th Annual Clean Gulf Conference & Exhibition; Houston, TX.
5. Nony, P. and Cobb, H. (2017) "Case Study: Ash Coulee Incident, Belfield, ND" Presented at the 27th Annual Clean Gulf Conference & Exhibition; Houston, TX.
6. Nony, P. and McKercher, W. "Vapor Intrusion." Platform talk presented to the Mississippi Manufacturers Association's 2016 Environmental & Safety Conference and Expo; Philadelphia, MS.
7. Nony, P. and Brady, P. (2016) "Community Air Quality Data During Accidental Release and Combustion of Crude Oil: Case Study of

Crude Oil Train Derailments." Presented at the Clean Pacific Conference and Exhibition, Seattle, WA.

8. Nony, P., McKercher, W., Hess, T, and Scribner, K. (2016) "Introduction to Vapor Intrusion." Presented at the Mississippi Department of Environmental Quality (MDEQ), Jackson, MS.
9. Nony, P. and Brady, P. (2016) "Air monitoring results from crude oil derailments and fires." Presented to the USEPA Region 10 Regional Response Team Northwest Area Contingency Committee Meeting, Boise, ID.
10. Nony, P. (2016) "Environmental, Energy, and Fracking: Regulatory, Compliance, and Litigation Issues in the Energy and Fracking Industries- A Toxicology Perspective." Presented at the American Bar Association Toxic Torts & Environmental Law Committee's 25th Annual Spring CLE Meeting, Phoenix, AZ.
11. Nony, P. (2016) "Preparing for Man-Made Catastrophes." Presented at C4: The CATIQ Canadian Catastrophe Conference, Toronto, ON, Canada.
12. Nony, P. (2015) "Efficacy of Shelter-In-Place Measures in Large-Scale Releases of Anhydrous Ammonia." Presented at the Ammonia Safety & Training Institute (ASTI) 32-Hour Ammonia Training; Watsonville, CA.
13. Nony, P. (2015) "Health & Physiology: A discussion on how the human body reacts when exposed to both common and hazardous chemicals." Keynote speech at the 7th annual Central Valley Chemical Safety Day Conference; Bakersfield, CA.
14. Nony, P. (2014) "Efficacy of Shelter-In-Place Measures in Large-Scale Releases of Anhydrous Ammonia." Presented at the Ammonia Safety & Training Institute (ASTI) 32-Hour Ammonia Training; Watsonville, CA.
15. Nony, P. (2014) "Incident Study: Crude Oil Train Derailments & Fires." Presented at the 21st Annual Advanced Flamable Liquid Firefighting Foam Technology Workshop; Beaumont, TX.
16. Nony, P. and Buckholtz, D. (2014) "Case Study: Minot, ND. Presented at the 27th Annual AAR/BOE Hazmat Seminar;" Addison, TX.
17. Paul Nony (2013). "Best Practices in Emergency Response Air Monitoring." Northern California Community Awareness in Emergency Response (CAER) Industrial Hygiene Group, Rodeo, CA.
18. Paul Nony (2013). "Case Studies of Non-Accident Release (NAR) Chemical Incidents." 2nd Semi-annual Federal Railroad Association, Railroad HazMat Conference, Reno, NV.
19. Paul Nony (2012). "Case Study: Well Blowout Response Air Monitoring - Wyoming." Shale Envirosafe Conference, New Orleans, LA.
20. Paul Nony (2012). Presentation titled, "Principles of Chemical Emergency Response" presented at the PEMEX Sexto Seminario Internacional De Characterizacion Y Remediacion De Sitios Impactados Por Hidrocarburos 2012, Mexico City, Mexico.
21. Paul Nony (2012). Presentation titled, "Industrial Hygiene in Chemical Emergency Response" presented to the ARKLATEX STEPS group in Marshall, TX.
22. Paul Nony (2012). Presentation titled, "Monitoring During a Chemical Spill" presented at the 25th Annual TCC/ACIT EHS Seminar in Galveston, TX.
23. Romano DeSimone, Paul Kurzanski, and Paul Nony (2012). Presentation titled, "Case Study: Painesville" presented at the 25th Annual AAR/BOE Hazardous Material Seminar, St. Louis, MO.
24. Paul A. Nony (2012). Invited lecture titled, "Air Monitoring, HazCom, and Risk Communication in Emergency Response" presented before the Texas Chemical Council Occupational Health and Safety Committee, LaPorte, TX.
25. Florine Clark, Scott Maris, Paul Nony, and Frederick Rom (2011). Panel discussion titled "When the Unthinkable Happens: Preparing for Industrial Catastrophes." Presented at the Annual Meeting of the Association of Corporate Counsel, Denver, CO.
26. Paul Nony (2011). "Effective Monitoring and Protection of Workers and the Community During Waterway Chemical Spills." Presented at the 28th Annual Virginia Hazardous Materials Conference & Expo, Hampton Roads, VA.
27. Paul A. Nony (2011). Invited lecture titled, "Case Studies in Managing Large-Scale Chemical Emergency Responses" presented at the PEMEX Quinto Seminario Internacional De Characterizacion Y Remediacion De Sitios Impactados Por Hidrocarburos 2011, Mexico City, Mexico.
28. Paul A. Nony (2010). Invited lecture titled, "Integrating Air Monitoring into Incident Command" presented at the 2010 California Air Response Planning Alliance (CARPA) Summit- Air Response Training Program in Sacramento, CA.
29. Paul A. Nony and Cory Davis (2010). Invited lecture titled, "Protection of Workers and Communities Affected by Waterway Oil Spills" presented to the 10th Reunion Annual Seguridad, Salud y Proteccion Ambiental de PEMEX, Veracruz, Mexico.
30. Paul A. Nony (2009, 2010). Invited lectures titled "Toxicology of Ammonia" and "Efficacy of Shelter-In-Place Methods" presented at the Ammonia Safety and Training Institute's 32-hr "Managing Ammonia Emergencies" course in Castoville, CA.
31. Paul A. Nony (2009, 2010, 2011). Invited course lectures titled, "Toxicology for the Emergency Responder", "Air Monitoring", and "Selection of Personal Protective Equipment and Chemical Protective Clothing" presented at the Texas Engineering Extension Service (TEEX) Emergency Response Training Center in College Station, TX.
32. Paul A. Nony (2008, 2009, 2010, 2011). Invited course lectures titled, "Toxicology for the Emergency Responder", "Air Monitoring", and "Selection of Personal Protective Equipment and Chemical Protective Clothing" presented at the Transportation

Technology Center, Inc.'s Security and Emergency Response Training Center in Pueblo, CO.

33. Paul A. Nony (2009). "Establishing Community and Responder Action Levels" presented in the session titled, "Toxicology of Intentional and Unintentional Disasters" at the 48th Annual Meeting of the Society of Toxicology in Baltimore, MD.
34. Paul A. Nony (2009). "Public Health Impacts of Volcanic Activity" presented in the session titled, "Toxicology of Intentional and Unintentional Disasters" at the 48th Annual Meeting of the Society of Toxicology in Baltimore, MD.
35. Paul A. Nony (2009). Invited lecture titled, "Toxicology Support: Aiding Emergency Responders and Communities Impacted by Chemical Emergencies" presented at the USEPA Region 6 Local Emergency Planning Committee (LEPC) Conference in Corpus Christi, TX.
36. Paul A. Nony (2008) Invited lecture titled, "Hazards of Clandestine Methamphetamine Labs and Basic Toxicology for Fire Investigators" presented to the Mississippi Fire Investigators Association conference in Natchez, MS.
37. Paul A. Nony, Michael Austin, and Harry Hopes III (2008). Invited lecture titled, "Support: Aiding Emergency Responders and Communities Impacted by Chemical Emergencies" presented in partnership with CSX Transportation at the USEPA Region 3 Emergency Preparedness Conference in Richmond, VA.
38. Paul A. Nony (2008). Invited panelist and speaker at California Air Response Planning Alliance (CARPA) Summit titled, "Air Quality in Emergency Response: Monitoring, Modeling, Messaging and Media" Sacramento, CA.
39. Paul A. Nony (2007). Session Moderator for: "Emerging Quantitative Tools and Practices for Assessing Exposure", a platform session presented to the California Pollution Control Officers Association (CAPCOA) special meeting e titled, "Health Impacts of Air Pollution on Communities." September 19, 2007, Carson, CA.
40. Paul A. Nony (2006). Toxicology Emerging from the Laboratory: Applying Scientific Principles to Real-World Chemical Problems. Hendrix College, Conway, AR.
41. Paul A. Nony (2005). Environmental Medicine: Facts and Fiction about Chemicals and Health. Presented to senior students in the Environmental Medicine course in the College of Nursing at the University of Arkansas for Medical Sciences, Little Rock, AR.
42. Paul A. Nony (2005). The Resource Conservation and Recovery Act (RCRA). Presented to masters and doctorate level students in the Toxicology and Government Regulations course at the University of Arkansas for Medical Sciences, Little Rock, AR.
43. Paul A. Nony (2004). Introduction to the Resource Conservation and Recovery Act (RCRA). Presented to students in Toxicology and Government Regulations course, UAMS, Little Rock, AR.
44. Paul A. Nony, Mike Feamster, Glenn C. Millner, and Alan C. Nye (2004). Issues in Ecological and Human Health Risk Assessment. Presented to Remediation Staff of Burlington Northern Santa Fe Railroad, Fort Worth, TX.
45. Paul A. Nony (2004). Career Options in Toxicology for Biology Majors. Presented to Hendrix Biology Society, Hendrix College, Conway, AR.
46. Paul A. Nony (2003). Environmental Careers Panel, Invited Panelist, Hendrix College, Conway, AR.
47. Paul A. Nony (2003). Careers in Health-Related Professions, Invited Panelist, Hendrix College, Conway, AR.
48. Paul A. Nony (2002). The role of lipoxygenases in eicosanoidstimulated tumor cell adhesion to type IV collagen. Presented to the Laboratory of Molecular Carcinogenesis, NIEHS, RTP, NC.
49. Paul A. Nony (2002). 15-Lipoxygenase-2 mediates arachidonic acid-stimulated adhesion of human breast carcinoma cells to type IV collagen. Presented to the 9th International Congress of the Metastasis Research Society, Chicago, IL.
50. Paul A. Nony (2001). The effects of collagens and integrins on physiological repair in renal cells. Presented to the Department of Biology, Hendrix College, Conway AR.
51. Paul A. Nony (2001). The role of collagen IV and collagenbinding integrins in renal cell repair following sublethal toxicant injury. Presented to the Laboratory of Molecular Carcinogenesis, NIEHS, RTP, NC.
52. P.A. Nony, G. Nowak, and R.G. Schnellmann (2000) Ascorbic acid-stimulated deposition of collagen IV is associated with repair of renal cell functions following sublethal injury. Abstract presented by poster at Contemporary Concepts in Toxicology: Mechanisms of Nephrotoxicity and Nephrocarcinogenicity (Martha's Vineyard, MA) and at the Arkansas Toxicology Symposium (Little Rock, AR).
53. P.A. Nony, G. Nowak, and R.G. Schnellmann (2000). Ascorbic acid-stimulated deposition of collagen IV is associated with repair of renal cell functions following sublethal injury. South Central Chapter/Society of Toxicology Annual Meeting (ULM, Monroe, LA).
54. P.A. Nony, G. Nowak, and R.G. Schnellmann (1999). Disruption of collagen type IV synthesis in renal proximal tubular cells by the nephrotoxicant dichlorovinyl-L cysteine. 1st Annual Seager-Braswell Science Symposium (UAMS, Little Rock, AR).

Doctoral Dissertation:

1. P. Nony. "Mechanisms Of Renal Cell Repair Following Acute Toxicant Injury." Dissertation (Ph.D.) - University of Arkansas for Medical Sciences, Little Rock, AR, 2001.

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Previous Testimony of Paul Nony, Ph.D., CIH, CSP

In the United States District Court for the District of Colorado
Janet Chi, et at. V Weyerhauser Company
No. 1:17-cv-02230-CMA-MEH
Deposition Testimony May 9, 2019

In the Circuit Court of Clay County, State of Missouri, Circuit Civil Division
John Thompson v BNSF Railway
No. 18CY-CV07008
Deposition Testimony August 21, 2019

In the Superior Court of the State of California, County of Los Angeles, Spring Street Courthouse
Candace Carmichael v Resco Products, et al.
No. BC711670
Deposition Testimony September 9, 2019

In the Superior Court of the State of California, County of San Francisco
Douglas Bell v Campbell Construction, et al.
No. CGC-14-276288
Deposition Testimony October 9, 2019

In the Superior Court of the State of California, County of San Alameda
Linda and Mark O'Hagan v Johnson & Johnson, et al.
No. RG19019699
Deposition Testimony November 8, 2019

In the Commonwealth of Kentucky, Gaves Circuit Court
Carolyn and Latta Wiman v Johnson & Johnson, et al.
No. 18-CI-00181
Deposition Testimony November 12 and December 2, 2019

In the District Court of Harris County, Texas, 151st Judicial District
Marissa Cooper v Thor Industries, et al.
No. 2017-12607
Deposition Testimony December 18, 2019

In the Civil Court for the Parish of Orleans, State of Louisiana
Lanny Roy, Jr. V PPG Industries, et al.
No. 2019-4270
Deposition Testimony January 22, 2020

In the Superior Court of the State of California, County of Tulare – Visalia Division
Dennis Jordan V Union Pacific Railroad
No. VCU277122
Trial Testimony February 25, 2020

In the Superior Court of the State of California, County of Los Angeles
Carol and Wayne Lebrecht v Johnson & Johnson, et. al.
No. BC700769
Deposition Testimony March 13, 2020

In the Court of Common Pleas for the Fifth Judicial Circuit
Richard Knight v Greenwood Mills, et. al.
No. 2019-CP-38-1045
Deposition Testimony August 18, 2020

In the Court of Superior Court of the State of Washington, County of King
Wendi and Richard Hirshberg v Johnson & Johnson, et. al.
No. 20-2-05603 SEA
Deposition Testimony February 25, 2021

In the Superior Court of the State of Washington, County of King
Wendi and Richard Hirshberg v Johnson & Johnson, et. al.
No. 20-2-05603 SEA
Deposition Testimony February 25, 2021

In the United States District Court, Southern District of Ohio, Western Division
Brent Adkins v Marathon Petroleum Company, LP
No. 1:17-cv-643
Deposition Testimony March 11, 2021

In the Civil District Court for the Parish of Orleans, State of Louisiana
Vita Chenet v Johnson & Johnson, et. al.
No. 20112536
Deposition Testimony March 18, 2021

In the Superior Court of the State of Washington for King County
Wendy and Richard Hirshberg v Johnson & Johnson, et. al.
No. 20-2-05603-1
Deposition Testimony April 9, 2021

In the Superior Court of the State of California, County of Alameda
Christina Prudencio v Johnson & Johnson, et. al.
No. RG20061303
Deposition Testimony April 12, 2021

In the Superior Court of the State of California, County of Alameda
Nedelka Vanklive v Johnson & Johnson, et. al.
No. RG20062734
Deposition Testimony June 28, 2021

In the United States District Court for the District of New Jersey
Robert Manz v Johnson & Johnson, et. al.
Docket No. 3:18-CV-14083
Deposition Testimony July 21, 2021

In the Superior Court of the State of California, County of Alameda
Christina Prudencio v Johnson & Johnson, et. al.
No. RG20061303
Trial Testimony July 28-29, 2021

In the Circuit Court of Cook County, Illinois County Department, Law Division
Stephen Davis v. BNSF Railway Company
Law No. 2018 L 7891
Deposition Testimony August 16, 2021

In the United States District Court Southern District of Ohio Eastern Division at Columbus
Joseph O'Byrne v. Weyerhaeuser et al.
Case No. 2:19-cv-02493-ALM
Deposition Testimony October 20, 2021

In the United States District Court for the Central District of Illinois
Judith Sherman v. BNSF Railway Company
Civil Action No.: 1-17-cv-1192
Deposition Testimony November 30, 2021

In the Circuit Court of the Ninth Judicial Circuit Knox County, Illinois
Jan Holeman v. BNSF Railway Company
No. 20LL0040
Deposition Testimony June 2, 2022

In the United States District Court for the Middle District of Louisiana
Joanne Reulet et al. v. Lamorak Ins. Co, et al.
Civil Action No. 3:20-cv-00404-BAJ-EWS
Deposition Testimony June 29, 2022

In the Civil District Court for the Parish of Orleans
Caroyln Amy et al. v. PPG, et al.
No. 2021-719
Deposition Testimony December 1, 2022

In the Civil District Court for the Parish of Orleans
Clarence Kenneth Lipscomb v. Jacobs Constructors, et al.
Division B No. 2022-6461
Deposition Testimony January 27, 2023

In the Superior Court of the State of California County of Alameda
Morgan Hall, II and Leah A Hall v. J.T. Thorpe & Son, et al.
Case No. 22CV012856
Deposition Testimony February 10, 2023

In the Superior Court of the State of California County of Alameda
Kathie Magdaleno, as successor-in-interest to Lawrence J. Magdaleno, and Andrea L. Bottazzo v. J.T. Thorpe & Son, et al.
Case No. RG19046904
Deposition Testimony April 25, 2023

In the Superior Court of the State of California County of Alameda
Mollie Damron v. JT Thorpe & Son, Inc et al.
Case No. 22CV021433
Deposition Testimony June 28, 2023

In the Circuit Court of the Fourth Judicial Circuit Jefferson County, Kentucky
Matthew Streck v. Johnson & Johnson et al
Case No 21-CI-06290
Deposition Testimony August 15, 2023

In the Superior Court of the State of Washington in and For the County of King
G. Ruth Alexander-Jones v. Johnson & Johnson et al
Case No 22-2-18669
Deposition Testimony September 13, 2023

In the Superior Court of California, County of Alameda
Marlin Eagles and Georgia Eagles v. Johnson & Johnson et al
Case No 22CV018294
Deposition Testimony October 4, 2023

In the Civil District Court for the Parish of Orleans, State of Louisiana, Section 8
Larry Richard v. PPG Industries, INC., et al
Case No 2022-05144
Deposition Testimony March 29, 2024

In the Circuit Court of Tuscaloosa County, Alabama
Jaimey Blankenship, as Personal Representative of the Estate of Cheryl Blankenship, v. Warrior Met coal Mining, et al
Case No. CV-2020-000043
Deposition Testimony April 15, 2024

Appendix B

Documents Received

1.0 PLEADINGS

- Plaintiffs' First Amended Master Long Form Complaint and Jury Demand (dated March 16, 2017)
- Defendants Johnson & Johnson and Johnson & Johnson Consumer Inc.'s Memorandum of Law in Support of Motion to Exclude Expert Opinions of Ghassan Saed (dated May 7, 2019)
- The Plaintiffs' Steering Committee's Memorandum of Law in Response and Opposition to Defendants Johnson & Johnson and Johnson & Johnsons Consumer Inc.'s Motion to Exclude Expert Opinions of Ghassan Saed (dated May 29, 2019)
- Defendants Johnson & Johnson and Johnson & Johnson Consumer Inc.'s Reply in Support of Motion to Exclude Expert Opinions of Ghassan Saed (dated June 17, 2019)
- Defendants Johnson & Johnson and Johnson & Johnson Consumer Inc.'s Post-Daubert Hearing Brief (dated October 7, 2019)
- Linda R. Bondurant - Plaintiff Profile Form, undated
- Linda R. Bondurant - Second Amended Plaintiff Profile Form
- Hilary T. Converse - Second Amended Plaintiff Profile Form
- Hilary T. Converse - Plaintiff profile form
- Anna Gallardo - Plaintiff profile form
- Carter Judkins - Plaintiff profile form
- Carter Judkins - Document Production Chart - First Amended Plaintiff Profile Form
- Tamara Newsome - Plaintiff profile form
- Pasqualina Rausa - Plaintiff profile form

2.0 DEPOSITIONS

- Transcript of the Videotaped Deposition of John Hopkins, PhD (dated April 11, 2018)
- Transcript of the Continued Videotaped Deposition of John Hopkins, PhD (dated April 12, 2018)
- Examination of Matthew Sanchez, PhD in Von Salzen v. American International Industries, Inc. et al. (dated September 21, 2018)
- Examination of Matthew Sanchez, PhD in Von Salzen v. American International Industries, Inc. et al. PM Session (dated September 21, 2018)
- Examination of Matthew Sanchez, PhD in Von Salzen v. American International Industries, Inc. et al. AM Session (dated September 24, 2018)
- Deposition of William E. Longo, PhD in Leavitt v. Johnson & Johnson et al. (dated November 6, 2018)
- Deposition of William E. Longo, PhD in Leavitt v. Johnson & Johnson et al., Volume II (dated November 27, 2018)
- Deposition of William E. Longo, PhD in Leavitt v. Johnson & Johnson et al., Volume III (dated December 5, 2018)
- Videotaped Deposition of Laura Plunkett, PhD, DABT (dated December 19, 2018)
- Videotaped Deposition of Michael , PhD (dated January 4, 2019)
- Videotaped Deposition of Arch I. Carson, MD, PhD (dated January 19, 2019)

- Videotaped Deposition of Judith Zelikoff, PhD (dated January 21, 2019)
- Videotaped Deposition of Ghassan Saed, PhD (dated January 23, 2019)
    - Deposition Exhibits of Ghassan Saed, PhD
- Continued Videotaped Deposition of Ghassan Saed, PhD (dated Febrary 14, 2019)
- Videotaped Deposition of Cheryl Saenz, MD (dated March 13, 2019)
- Daubert Hearing of Ghassan Saed, PhD, (dated July 22, 2019)
- Remote Oral Deposition of Hilary Converse (dated December 1, 2020)
- Remote via Zoom Deposition of Anne Carter Judkins (dated December 1, 2020)
- Remote Videotaped Deposition of Tamara Newsome (dated December 9, 2020)
- Remote Oral Deposition of Anna Gallardo (dated January 12, 2021)
- Remote Deposition of Pasqualina Rausa (dated January 27, 2021)
- Expert Deposition of Laura M. Plunkett, PhD, DABT (dated August 10, 2021)

3.0 EXPERT REPORTS

- Expert report of Dana M. Hollins, MPH, CIH in Kerkhof v. Brenntag North America, Inc. et al. (dated August 3, 2018)
- Expert report of Jennifer Sahmel, MPH, CIH, CSP in Allen v. Brenntage North America, et al. (dated September 11, 2018)
- Expert report of Dana M. Hollins, MPH, CIH in DeAugustinis v. Brenntag North America, Inc, et al. (dated October 12, 2018)
- Rule 26 Report of Michael M. Crowley, PhD Regarding the Fragrance Chemical Constituents in Johnson & Johnson Talcum Powder Products, dated November 12, 2018
    - Crowley Reliance materials
- Expert Report of William E. Longo, PhD & Mark W. Rigler, PhD The Analysis of Johnson & Johnson's Historical Baby Powder & Shower to Shower Products from the 1960's to the Early 1990's for Amphibole Asbestos (dated November 14, 2018)
- Rule 26 Expert Report of Rebecca Smith-Bindman MD, The Relationship Between Exposure to Perineal Talc Powder Products and Ovarian Cancer (dated November 15, 2018)
- Rule 26 Expert Report of Sarah E. Kane, MD (dated November 15, 2018)
- Rule 26 Expert Report of Daniel L. Clarke-Pearson, MD (dated November 16, 2018)
- Rule 26 Expert Report of Robert B. Cook, PhD (dated November 16, 2018)
    - Imerys and Johnson & Johnson Documents Cited in Cook Report
- Rule 26 Expert Report of Alan Campion, PhD (dated November 26, 2018)
- Rule 26 Expert Report of Arch Carson, MD, PhD, Talcum Powder and Ovarian Cancer (dated November 16, 2018)
- Expert Report of David A. Kessler, MD (dated November 16, 2018)
- Rule 26 Expert Report of Mark Krekeler, PhD (dated November 16, 2018)
    - Imerys and Johnson & Johnson Documents Cited in Krekeler Report
- Rule 26 Expert Report of Shawn Levy, PhD (dated November 16, 2018)
- Rule 26 Expert Report of Anne McTiernan, MD, PhD (dated November 16, 2018)

- Rule 26 Expert Report of Patricia G. Moorman, MSPH, PhD, Scientific Review of the Epidemiological Evidence on Talc Use and Ovarian Cancer (dated November 16, 2018)
- Rule 26 Expert Report of Laura M. Plunkett, PhD, DABT (dated November 16, 2018)
- Rule 26 Expert Report of Dr Ghassan Saed, Molecular basis for the association of talcum powder use with increased risk of ovarian cancer (dated November 16, 2018)
    - Exhibits A-C from Expert Report of Dr Ghassan Saed
- Rule 26 Expert Report of Jack Siemiatycki, MSc, PhD, Talcum Powder Use and Ovarian Cancer (dated November 16, 2018)
- Rule 26 Expert Report of Sonal Singh, MD, MPH, Talcum Powder Products and Risk of Ovarian Cancer (dated November 16, 2018)
- Rule 26 Expert Report of Ellen Blair Smith, MD (dated November 16, 2018)
- Rule 26 Expert Report of Judith Wolf, MD (dated November 16, 2018)
- Rule 26 Expert Report of April Zambelli-Weiner, PhD, MPH (dated November 16, 2018)
- Rule 26 Expert Report of Judith Zelikoff, PhD (dated November 16, 2018)
    - Ex. C (Zelikoff, Judith)
- William E. Longo, PhD and Mark W. Rigler, PhD. 2019 The Analysis of Johnson & Johnson's Historical Product Containers and Imerys' Historical Railroad Car Samples from the 1960's to the Early 2000's for Amphibole Asbestos: Supplemental Report (Dated January 15, 2019)
- Expert Report of William E. Longo, PhD and Mark W. Rigler, PhD. The Analysis of Johnson & Johnson's Historical Product Containers and Imerys' Historical Railroad Car Samples from the 1960's to the Early 2000's for Amphibole Asbestos, 2nd Supplemental Report (dated February 1, 2019)
    - Amphibole Asbestos Found in Historical Johnson's Baby Powder and Johnson's Shower to Shower Powder 1960 - 2000s and Talc Fibers Found in Historical J&J Cosmetic Talcum Powders 1960s - 2000s (Adapted from Longo and Rigler report, dated February 1, 2019)
- Rule 26 Report of H. Nadia Moore, PhD, DABT, ERT (dated February 25, 2019)
- Expert Report of Kelly Scribner Tuttle, PhD, CIH (dated February 25, 2019)
- Expert Report of Ann G. Wylie, PhD for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Benjamin G. Neel, MD, PhD for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Brooke Taylor Mossman, MS, PhD for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Cheryl Christine Saenz, MD for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Christian Merlo, MD, MPH for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Gregory Diette, MD, MHS for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Ie-Ming Shih, MD, PhD for General Causation Daubert Hearing (dated February 25, 2019)

- Expert Report of Jeff Boyd, PhD for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Karla Ballman, PhD for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Kevin Holcomb, MD, FACOG for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Laura Webb, PhD for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of M. Darby Dyar, PhD for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Mary Poulton, PhD for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Michael Birrer, MD, PhD for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of Robert J. Kurman, MD for General Causation Daubert Hearing (dated February 25, 2019)
- Expert Report of William E. Longo, PhD. MAS Project #M71166 Off-The-Shelf 2020 JBP Talcum Powder Analysis, Supplement Report 1 (dated September 29, 2020)
- Expert Report of William E. Longo, PhD. MAS Project #M7166 & M71180 Off-The-Shelf 2020 JBP Talcum Powder Analysis, Supplement Report 2 (dated December 8, 2020)
- Amended Expert Report of Laura M. Plunkett, PhD, DABT (dated June 30, 2021)
- Expert Report of George Newman, PhD (dated November 15, 2023)
- Expert Report of Bernard Harlow, PhD, and Kenneth Rothman, DrPH (dated November 15, 2023)
- Expert Report of Michele Cote, PhD, MPH (dated November 15, 2023)
- Amended Rule 26 Expert Report of William Sage, MD, JD (dated November 15, 2023)
- Amended Rule 26 Expert Report of Shawn Levy, PhD (dated November 15, 2023)
- Second Amended Expert Report of Anne Mctiernan, MD, PhD (dated November 15, 2023)
- Supplemental Expert Report of Sonal Singh, MD, MPH (dated November 15, 2023)
- Amended Expert Report of David A. Kessler, MD (dated November 15, 2023)
- Second Amended Rule 26 Expert Report of Judith Wolf, MD (dated November 15, 2023)
- Second Amended Expert Report of Jack Siemiatycki, MSc, PhD (dated November 15, 2023)
- Second Amended Expert Report of Rebecca Smith-Bindman, MD (dated November 15, 2023)
- Second Amended Expert Report of Laura Plunkett, PhD, DABT (dated November 15, 2023)
- Second Amended Rule 26 Expert Report of Daniel Clarke-Pearson, MD (dated November 15, 2023

4.0 LITERATURE/REPORTS/MISCELLANEOUS/COMMUNICATIONS

- Anderson et al. 2017. Assessment of Health Risk from Historical Use of Cosmetic Talcum Powder. Risk Analysis 37(5): 918-929
- Aylott et al. 1979. Normal use of levels of respirable cosmetic talc: preliminary study. International Journal of Cosmetic Sciences 1: 177-186
- Belotte et al. 2015. A Single Nucleotide Polymorphism in Catalase is Strongly Associated with OC Survival. PLOS ONE.
- Berry et al. 2000. Mortality from all cancers of asbestos factory workers in east London 1933-80. Occup Environ Med 57: 782-785.
- Boundy et al. Occupational exposures to non-asbestiform talc in Vermont. In Dust and Disease, edited by R. Lemen and J.M. Dement. Society for Occupational and Environmental Health.
- Centers for Disease Control and Prevention (CDC). 2021. What Are the Risk Factors for Ovarian Cancer?
- Coggiola et al. 2003. An update of a mortality study of talc miners and millers in Italy. American Journal of Industrial Medicine 44: 63-69.
- Communication from Robert Morris to Ghassan Saed, Re: Manuscript (dated July 20, 2020)
- Communication from Setsuko Chambers (Associate Editor, Reproductive Sciences) to Ghassan Saed, Re: Your Submission RESC-D-20-00635 (dated August 27, 2020)
- Communication from Salik Hussain, DVM, MS, PhD (Academic Editor, PLOS ONE) to Ghassan M. Saed, Re: PLOS ONE Decision: PONE-D-20-29874 (dated October 28, 2020)
- Communication from Barbara A. Goff, MD (Editor, Gynecolgic Oncology) to Ghassan M. Saed, Re: GYN-20-1870: Final Decision (dated February 2, 2021)
- Dement, et al. 1972. Fiber exposure during use of baby powders. National Institute for Occupational Safety and Health. NIOSH-00106056
- Egilman. Exhibit #355. Asbestos ovarian cancer dose estimates (undated)
- Exponent. 2013. Cosmetic Talc: Comparison of Glove Box and Chamber Data (dated June 11, 2013)
- Fletcher et al. 2017. Specific Point Mutations in Key Redox Enzymes Are Associated with Chemoresistance in Epithelial Ovarian Cancer. Free Radical Biology and Medicine 102: 122-132
- Fletcher et al. 2018. Talcum Powder Enhances Oxidative Stress in Ovarian Cancer Cells. Reproductive Sciences 25(1): 214A-215A
- Fletcher et al. 2018. Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer. Manuscript Submission to Gynecologic Oncology (GYN-18-1020)
- Fletcher and Saed. 2018. Talcum Powder Enhances Cancer Antigen 125 Levels in Ovarian Cancer Cells and in Normal Ovarian Epithelial Cells. Abstract presented at Society for Reproductive Investigation 65th Annual Scientific Meeting. March 6-10, 2018. San Diego, CA.
- Fletcher et al. 2019. Molecular Basis Supporting the Association of Talcum Powder Use with Increased Risk of Ovarian Cancer. Reproductive Sciences

- Fletcher et al. 2019. Molecular basis supporting the association of talcum powder use with increased risk for ovarian cancer. Manuscript Submission to Reproductive Sciences
- Fletcher et al. 2020. Letter to the Editor - Molecular Basis Supporting the Association of Talcum Powder Use with Increased Risk of Ovarian Cancer. Reproductive Sciences
- Gates et al. 2008. Talc use, variants of the GSTM1, GSTT1, and NAT2 Genes, and risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev 17(9)
- Gordon et al. 2014. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. International Journal of Occupational and Environmental Health
- Harper & Saed. 2018. Talc induces a pro-oxidant state in normal and ovarian cancer cells through gene point mutations in key redox enzymes. SGO Abstract submission
- Harper et al. 2020. Talcum powder induces malignant transformation of human primary normal ovarian epithelial cells but not human primary normal peritoneal fibroblasts. Gynecological Oncology 159: Figure 1
- Harper et al. Undated. Talcum powder induces malignant transformation of human primary normal ovarian epithelial cells but not human primary normal peritoneal fibroblasts. 297 – Poster Session
- Harper et al. 2020. Talcum powder induces malignant transformation of human primary normal ovarian epithelial cells but not human primary normal peritoneal fibroblasts. Gynecological Oncology 159: 79. Abstract
- Harper et al. 2021. Talcum powder induced malignant transformation in normal human primary ovarian epithelial cells. Submission to Minerva Ginecologica/Minerva Obstetrics and Gynecology (dated September 30, 2021)
- Harper et al. 2021. Talcum powder induces malignant transformation in normal human primary ovarian epithelial cells. Submission to Minerva Obstetrics and Gynecology (dated October 1, 2021)
- Hildick-Smith. 1976. The biology of talc. British Journal of Industrial Medicine 33: 217-229.
- IARC. 2012. IARC Monographs of the Evaluation of Carcinogenic Risks to Humans. Volume 100C: Arsenic, metals, fibres, and dusts.
- Lightfoot et al. 1972. An examination of Italian mine samples and relevant powders. University College, Cardiff.
- Longo et al. 2017. MAS Project 14-1852. Below the Waist Application of Johnson & Johnson Baby Powder (dated September 2017)
- Longo et al. 2018. MAS Project 14-1852. Below the Waist Application of Johnson & Johnson Baby Powder. Supplement Report #2 (dated January 2018)
- William E. Longo, PhD and Mark W. Rigler, PhD. 2018. Preliminary Analysis Report MAS Project #14-1683. Johnson's Baby Powder Sample Set (dated March 11, 2018)
- William E. Longo, PhD and Mark W. Rigler, PhD. 2018. Supplemental Expert Report & Analysis of Johnson & Johnson Baby Powder and Valeant Shower to Shower Talc Products for Amphibole Asbestos (dated March 11, 2018)
- Longo Exhibit #3 (Dated April 23, 2018)

- William E. Longo, PhD, et al. 2019. Johnson's Baby Powder Application to Baby During Diaper Change: A Work Practice Study (dated January 2019)
- Vitae of William E. Longo, PhD (dated November 22, 2017) William E. Longo, PhD. Testimony Listing (undated)
- William E. Longo, PhD. Testimony Listing (undated)
- Timothy J. McCarthy, PhD, DABT. Adding TEM to the Global Talc Specification (undated)
- Moon et al. 2011. Risk assessment of baby powder exposure through inhalation. Toxicology Research 27(3): 137-141
- NIOSH. 2011. Asbestos fibers and other elongate mineral particles: State of the Science and Roadmap for Research. Current Intelligence Bulletin 62.
- O'Brien et al. 2021. The association between douching, genital talc use, and the risk of prevalent and incident cervical cancer. Nature Scientific Reports 11:14836.
- F.D. Pooley. Undated. Report of the examination of rock samples from the Vermont Mine. University College, Cardiff.
- Pira et al. 2017. Mortality of talc miners and millers from Val Chisone, Northern Italy: an updated cohort study. JOEM 59(7): 659-664
- Rubino et al. 1976. Mortality study of talc miners and millers. Journal of Occupational Medicine 18(3): 186-193
- Rubino et al. 1979. Mortality and morbidity among talc miners and millers in Italy.
- Russell et al. 1979. The determination of respirable particles in talcum powder. Food and Cosmetic Toxicology 17: 117-122
- Saed et al. 2017. Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. Gynecologic Oncology 145: 595-602
- Saed et al., 2018. New Insights into the Pathogenesis of Ovarian Cancer: Oxidative Stress. IntechOpen
- Saed. Undated. SGO abstract Table 1 SNP gene mutation
- Saed. Undated. The role of talc powder exposure in ovarian cancer: mechanistic approach (Talc and EOC Project)
- Saed lab notebooks 000001-97
- Saed lab notebooks (dated 2019-2020)
- Saed et al. Undated. Talcum powder induces a malignant transformation in normal ovarian epithelial cells. Poster presentation.
- Matthew S. Sanchez, PhD. 2018. Preliminary Analytical Test Report of thirty-seven MAS Split Samples (dated April 23, 2018)
- Selevan et al. 1979. Mortality patterns among miners and millers of non-asbestiform talc: preliminary report. Journal of Environmental Pathology and Toxicology 2: 273-284.
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    - Johnson's Baby Powder Safety Data Sheet, dated July 10, 2015
    - Johnson's Baby Powder Formula 9883-052 Product Specification, dated October 5, 2012
- Johnson's Baby Powder Formula Declaration Report, dated December 3, 2009

Appendix C

Summary of Case-Control Studies of Consumer Talc Use and Ovarian Cancer

Table of Contents

1.0 CRAMER ET AL. (1982)

In 1982, Cramer et al. performed a case-control study of 215 women diagnosed with epithelial ovarian cancer between 1978 and 1981 and 215 controls in Boston, MA, to assess the relationship between genital talc use and ovarian cancer (Cramer et al., 1982). Information on talc use was obtained during interviews. When adjusting for parity and menopausal status, the authors found an increased risk among women with any perineal talc use (as a dusting powder or on sanitary napkins) (RR: 1.92; 95% CI: 1.27 – 2.89). When studying women who had both exposures, the authors found a relative risk of 3.28 (95% CI: 1.68 – 6.42). When adjusting for additional potential confounders (religion, marital status, education, ponderal index, age at menarche, parity, oral contraceptive or menopausal hormone use, and smoking history), the relative risk for any perineal talc use was found to be 1.61 (95% CI: 1.04 – 2.49). The authors noted the potential for selection bias among the controls due to a high refusal rate of 33% among the eligible potential controls.

2.0 HARTGE ET AL. (1983)

Hartge et al.'s 1983 case-control study of 135 women with epithelial ovarian cancer and 171 controls in Washington DC examined the association between talc use and risk of ovarian cancer (Hartge et al., 1983). Study participants were interviewed between 1974 and 1977 but questions about talc use were added after the study began. Excluding those not interviewed about talc use yielded the cases and controls identified previously. The authors found no association between any talc use and risk of ovarian cancer (RR: 0.7; 95% CI: 0.4 – 1.1). Additionally, no excess risk was found among women who used talc on a diaphragm (RR: 0.8; 95% CI: 0.4 – 1.4) or as a body powder (RR: 0.8; 95% CI: 0.5 – 1.2). When stratified by type of body powder application, an increased risk was found for women who used talc in the genital area (on genitals, sanitary napkins, or underwear; RR: 2.5; 95% CI: 0.7 – 10.0) but it was noted that the small number of exposed women yielded an unreliable estimate (7 cases and 3 controls). Potential confounders adjusted for included race, age, and gravidity. The authors reported potential limitations as selection or observation bias or confounding. They specifically noted that the difference in talc use reported between cases and controls as a potential bias however, they also found that cases and controls were equally likely to report douching which was believed to the subject to the same potential recall bias as talc use.

3.0 WHITTEMORE ET AL. (1988)

In 1988, Whittemore et al. studied the association between perineal talc use and ovarian cancer 188 cases of epithelial ovarian cancer (diagnosed between 1983 and 1985) and 539 controls (280 hospital controls and 259 population controls) in the San Francisco Bay Area (Whittemore et al., 1988). Study participants were interviewed about ever having used perineal talc on the perineum, sanitary napkins, or diaphragms and those who did were further questioned about frequency and duration of use. The authors found an insignificant increased risk for any talc use (any two of application to the perineum, sanitary napkins, or diaphragm; RR: 1.36; 95% CI: 0.91 – 2.04). When stratified by type of talc use, the authors also found an insignificant increased risk

for perineal talc use (RR: 1.45; 95% CI: 0.81 – 2.60) and diaphragm use (RR: 1.50; 95%: 0.63 – 3.58). No increased risk was found among women who applied talc to sanitary napkins (RR: 0.62; 95% CI: 0.21 – 1.80). Potential confounders adjusted for were parity and oral contraceptive use. No dose-response trend was found when reviewing long-term users (≥ 10 years) and never users (RR: 1.11; 95% CI: 0.74 – 1.65; P_{trend} = 0.61). No trend was found with increasing frequency of use – the relative risk for women who used talc at least 30 times per month was 1.30 (95%: 0.88 – 1.92; P_{trend} = 0.19). Reviews of frequency and duration of use were adjusted for parity.

4.0 BOOTH ET AL. (1989)

Booth et al.'s 1989 hospital-based case control study of 235 women diagnosed with epithelial ovarian cancer and 451 controls studied the association between genital talc use and ovarian cancer in the United Kingdom (Booth et al., 1989). Questions on talc use were introduced three months after the study began resulting in missing data for 18 cases and 17 controls. Women who reported daily genital talc use had an insignificant increased risk of ovarian cancer (RR: 1.3; 95% CI: 0.8 – 1.9) and no trend was found with increasing frequency of use (P_{trend} = 0.05). Potential confounders adjusted for were age and social class. It was noted that women were not asked about the duration of their talc use.

5.0 CHEN ET AL. (1992)

In 1992, Chen et al. reviewed talc use and risk of ovarian cancer in China in a case-control study of 112 cases of epithelial ovarian cancer diagnosed between 1984 and 1986 and 224 controls (Chen et al., 1992). When adjusted for education and parity, the authors found an insignificant increased risk among women who used talc as a dusting powder on the lower abdomen and perineum for at least three months (RR: 3.9; 95% CI: 0.9 – 10.6). It was noted that the small number of women who reported talc use (7 cases and 5 controls) made it impossible to distinguish between different types of exposures (as a dusting powder to the perineum, abdominal surgery, pelvic examinations, and occupational exposures).

6.0 HARLOW ET AL. (1992)

In 1992, Harlow et al. studied the risk of ovarian cancer among women who used genital talc in a case-control study of 235 women diagnosed with epithelial ovarian cancer between 1984 and 1987 and 239 controls in Boston, MA (Harlow et al., 1992). Interview questions regarding talc exposure included use in underwear, on sanitary napkins and diaphragms, application directly to the perineum, and via a husband's use of talc. No reliable information about talc use during diapering as an infant was gathered and women who used talc as a body powder outside of the perineum were considered nonexposed. The authors found an insignificant increased risk for any genital talc use (OR: 1.5; 95% CI: 1.0 – 2.1) and a significant increased risk for direct application to the genital area (included combinations with sanitary napkins or underwear; OR: 1.7; 95% CI: 1.1 – 2.7). Potential confounders adjusted for included parity, education, marital status, religion, use of sanitary napkins, history of douching, age, and weight. When examining frequency and duration of use, the authors reported that "the risk for ovarian cancer increased significantly with increasing frequency of applications per

month [P_{trend} = 0.046]" with the greatest risk being among women who used talc at least once per day (OR: 1.8; 95% CI: 1.1 – 3.0). When including years of use, a P_{trend} of 0.07 was found. When looking at total applications (excluded use after a hysterectomy of tubal ligation and use during nonovulatory months [taking oral contraceptives, while pregnant or breastfeeding, or occurring after menopause]), the authors found an increased risk associated with more than 10,000 applications (P_{trend} = 0.015). The authors concluded that "because the overall association between genital use of talc and ovarian cancer remains weak, it is unlikely that this exposure-disease pathway is the principal one involved in ovarian cancer etiology".

7.0 ROSENBLATT ET AL. (1992)

in 1992, Rosenblatt et al. conducted a hospital-based case-control study to examine the association between fiber exposure and incidence of epithelial ovarian cancer among 77 cases and 46 controls in Baltimore, MD, between 1981 and 1985 (Rosenblatt et al., 1992). Information regarding genital fiber exposure (defined as asbestos, talc, and fiberglass) was obtained via questionnaire. The authors reportedly attempted to estimate dose by adding the number of years for each type of exposure but noted that "since many of these exposures occurred at the same time, these variables should be considered crude measures of dose rather than the true length of exposure". An increased risk was found among women who had genital fiber exposure from various sources for a cumulative exposure of at least 37.4 years (OR: 2.35; 95%: 0.95 – 5.80). Specifically, among women who applied talc to the genital area after bathing, an odds ratio of 1.7 (95% CI: 0.7 – 3.9; adjusted for tobacco use, ovulatory time period, number of pregnancies, family history of cancer, obesity, education, personal history of cancer, marital status, religion, and contraceptive use) was found among women with any genital fiber use. A significant increased risk was found among women who used talc on sanitary napkins (OR: 4.8; 95%: 1.3 – 17.8; adjusted for number of live births and education)) while an insignificant increased risk was found for talc use with a diaphragm (OR: 3.0; 95%: 0.8 – 10.8; adjusted for highest weight one year prior to diagnosis).

8.0 CRAMER AND XU (1995)

Cramer and Xu (1995) combined data from two previous case-control studies (215 cases and 215 controls from 1978 – 1981 and 235 cases and 239 controls from 1984 – 1987 for a total of 450 cases and 454 controls) and reviewed the association between talc use and ovarian cancer in the greater Boston, MA, area (Cramer & Xu, 1995). For women with any talc use, an odds ratio of 1.6 (95% CI: 1.2 – 2.1) was found. Data regarding talc exposure was limited as the primary objective of this study was to examine the association between ovarian cancer and hysterectomy or tubal ligation. The authors noted that the odds ratio for a hysterectomy or tubal ligation for the risk of ovarian cancer was 1.1 (95% CI: 0.6 – 2.1 among talc users.

9.0 CHANG AND RISCH (1997)

In 1997, Chang and Risch studied the association between talc use and ovarian cancer among 450 cases diagnosed between 1989 and 1992 and 564 controls in Canada (Chang & Risch, 1997). Data on talc use was obtained from a questionnaire. Potential confounders adjusted for included age, oral contraceptive use, number

of full-term pregnancies, average duration of breastfeeding, tubal ligation, hysterectomy, and family history of breast or ovarian cancer. A significant increased risk was found among women with any talc exposure (OR: 1.42; 95% CI: 1.08 – 1.86) and an increased risk was found among women who applied talc to the perineum after bathing (OR: 1.312; 95% CI: 1.00 – 1.73). An insignificant increased risk was found for talc used with sanitary napkins (OR: 1.262; 95% CI: 0.81 – 1.96). When reviewing frequency and duration of use, the authors found a borderline significant association between duration of talc exposure and risk of ovarian cancer (OR: 1.091; 95% CI: 0.98 – 1.21) and no significant association was found for frequency of exposure and risk (OR: 0.89; 95% CI: 0.74 – 1.07).

10.0 COOK ET AL. (1997)

In 1997, Cook et al. conducted a case-control study of 313 ovarian cancer cases (diagnosed between 1986 and 1988) and 422 controls in Washington study the association of ovarian cancer with perineal powder use (Cook et al., 1997). Powders were grouped as cornstarch, talcum powder, baby powder, deodorant powder, and scented body/bath powder. Women who reported any genital powder use had a relative risk of 1.5 (95% CI: 1.1 – 2.0) while women who exclusively used talc in the genital area had a relative risk of 1.2 (95% CI: 0.6 – 2.5). Women who may have used a variety of powders, including any talc, had a relative risk of 1.6 (95% CI: 0.9 – 2.8). During their analyses, the authors adjusted for age. It was reported that “no specific type of powder used for perineal dusting, diaphragm storage, or on sanitary napkins was strongly related to ovarian cancer risk”.

11.0 GREEN ET AL. (1997)

Also in 1997, Green et al. reviewed the association between perineal talc use and ovarian cancer among 824 cases diagnosed between 1990 and 1993 and 855 controls in Australia (Green et al., 1997). Women with a history of ovarian cancer and bilateral oophorectomy were excluded from the study. The authors reported a “modest association” among women who had used perineal talc (RR: 1.3; 95% CI: 1.1 – 1.6). It was also reported that “there was no additional effect of longer duration of talc use nor was there any relation to reported age when talc was first used in the perineal region”. The authors reported a reduced risk among women who had undergone a tubal ligation (RR: 0.61; 95% CI: 0.46 – 0.85) or hysterectomy (RR: 0.64; 95% CI: 0.48 – 0.85) and opined that “pelvic contaminants” including talc gain access to the peritoneal cavity through patent reproductive tracts and “may enhance the malignant transformation of ovarian surface epithelium”.

12.0 ELTABBAKH ET AL. (1998)

Eltabbakh et al.’s (1998) examined the association between perineal talc use and incidence of ovarian cancer among 503 ovarian cancer cases and 50 extraovarian peritoneal cancer cases (functioned as the controls) who were diagnosed between 1982 and 1996 in New York (Eltabbakh et al., 1998). Very little was said regarding talc use: “Significantly fewer women with extraovarian primary peritoneal cancer ever used perineal talc than their counterparts with primary epithelial ovarian cancer (26.0% versus 48.1%, P = .003)”.

13.0 GODARD ET AL. (1998)

In 1998, Godard et al. conducted a case-control study of 170 cases of ovarian cancer and 170 controls who were enrolled in the study between 1995 and 1996 in Canada (Godard et al., 1998). An insignificant increased risk was found for women who had ever used perineal talc (RR: 2.49; 95% CI: 0.94 – 6.58). The authors concluded that "although there are reports of talc embedded in human ovarian tissue and of talc migrating through the human female reproductive tract, the literature reviewed does not provide any convincing evidence that pure cosmetic talc, when used as intended, presents a health risk to women".

14.0 NESS ET AL. (2000)

Ness et al. (2000) studied 767 cases of ovarian cancer (identified between 1994 and 1998; diagnosed within six months prior to the interview) and 1,367 controls from the Delaware Valley area (Ness et al., 2000). The authors found a significant increased risk of ovarian cancer among women who applied talc to perineal area (OR: 1.5; 95% CI: 1.1 – 2.0), sanitary napkins (OR: 1.6; 95% CI: 1.1 – 2.3), and underwear (OR: 1.7; 95% CI: 1.2 – 2.4). Additionally, talc exposure from use on diaphragms and/or cervical caps (OR: 0.6; 95% CI: 0.3 – 1.3) and use by a male partner (OR: 1.0; 95% CI: 0.7 – 1.4) "did not appear to alter risk by much". Potential confounders adjusted for included age, number of pregnancies, family history of ovarian cancer, race, use of oral contraceptives, tubal ligation, hysterectomy, and breastfeeding. When duration of use was reviewed, the authors also noted that this "was not clearly related to risk" (OR: 1.2; 95% CI: 1.0 – 1.5; for at least ten years of use).

15.0 LANGSETH AND KJAERHEIM (2004)

In 2004, Langseth and Kjaerheim examined 35 cases of ovarian cancer and 121 controls that were selected and interviewed (interview respondents included self-respondents, spouse, child/sibling, or "other") from a cohort of asbestos, talc, and total dust exposed pulp and paper workers in Norway during the follow-up period from 1953 until 1999 (Langseth & Kjærheim, 2004). Of the women who reported ever having used talc for personal hygiene (used on diapers, sanitary napkins, non-genital area, or husband's use in the genital area), an odds ratio of 1.15 (0.41 – 3.21) was found. Notably, as indicated above, most information obtained during the interview process about the cases was gathered from relatives – "71.4% of the patients and 28.6% of the controls were dead; therefore, much more information about the cases was collected from relatives than for the controls". The authors reported that "the questions on hygienic talc use resulted in many missing values among the proxy respondents". It should also be noted that having ever used talc for personal hygienic purposes was reported among a small number of women (12 cases and 53 controls).

16.0 MILLS ET AL. (2004)

Mills et al.'s 2004 case-control study examined the association between perineal talc use and incidence of ovarian cancer among 256 cases and 1,122 controls in California who were interviewed between 2000 and 2001 (Mills et al., 2004). It was found that ever having used talc in the genital area was associated with a significant increased risk of ovarian cancer (OR: 1.37; 95% CI: 1.02 – 1.85). The authors found an increased risk for frequency

of use for women who used talc four to seven times per week (OR: 1.74; 95% CI: 1.14 – 2.64; P_{trend} = 0.015) however, this was not a monotonic upward trend as risk decreased between women who used perineal talc rarely/several times per month and women who used one to three times per week (ORs from 1.34 to 1.16). When examining duration of use, the authors also found an increased risk however, "the pattern was also not clear-cut in that the point estimate peaked among those reporting 4 – 12 years of use and declined somewhat among those reporting longer duration of use (p for trend = 0.045)". The authors also reported an uneven association between ovarian cancer risk and cumulative use of perineal talc (P_{trend} = 0.051). Potential confounders adjusted for included age, race, duration of oral contraceptive use, and breastfeeding. The authors concluded that no dose-response association was found.

17.0 CRAMER ET AL. (2005)

In 2005, Cramer et al. reviewed the association between talc use and incidence of ovarian cancer in a case-control study of 668 ovarian cancer cases and 705 controls in Massachusetts and New Hampshire from 1998 to 2003 (Cramer et al., 2005). While the primary objective of the study was to assess the relationship between anti-MUC1 antibodies and ovarian cancer (it was hypothesized that the nonuse of talc is one of the factors for predicting antibodies and that the events predicting the antibodies would be inversely associated with ovarian cancer risk), an insignificant increased risk was found among women who used talc in the genital area (OR: 1.16; 95% CI: 0.90 – 1.49). Potential confounders adjusted for included age, parity, non-white race, and Jewish religion. The authors also found that genital talc use was associated with decreased levels of anti-MUC1 antibodies.

18.0 GATES ET AL. (2008)

In 2008, Gates et al. conducted a case-control study of 1,385 ovarian cancer cases (1,175 from the New England Case-Control Study [NECC] and enrolled between 1992 – 1997 and 1998 - 2003; 210 from the Nurses' Health Study [NHS] and enrolled in 1976 with follow-up through 2004) and 1,802 controls (1,202 from the NECC and 600 from the NHS) to review the association between genital talc use and ovarian cancer (Gates et al., 2008). Questions about talc use were included in both phases of the NECC but questions about talc use were not included in the NHS until the 1982 questionnaire. In the pooled analysis, the authors reported a significant increased risk for regular genital talc use (at least once per week) and all ovarian cancer (RR: 1.36; 95% CI: 1.14 – 1.63) and for increasing frequency of use (P_{trend} = <0.001). When stratified by histotype in the pooled analysis, a significant increased risk was found for serous invasive tumors (RR: 1.60; 95% CI: 1.26 – 2.02; increasing frequency P_{trend} = <0.001) and an insignificant increased risk for the endometroid (RR: 1.41; 95% CI: 0.97 – 2.05) and mucinous (RR: 1.28; 95% CI: 0.85 – 1.92) subtypes. Potential confounders adjusted for included age, oral contraceptive use, parity, tubal ligation, body mass index, and duration of post-menopausal hormone use.

19.0 MERRITT ET AL. (2008)

Also in 2009, Merritt et al. studied 1,576 cases of epithelial ovarian cancer diagnosed between 2002 and 2005 and 1,509 controls in Australia (Merritt et al., 2008). Among women who had ever used perineal talc, a significant

increased risk in all ovarian cancer was found (OR: 1.17; 95% CI: 1.01 – 1.36). It was noted that this analysis was restricted to years of use while the reproductive tract was intact. When examining duration of use, the authors reported no clear trend of increasing risk although the trend was of borderline significant (P_{trend} = 0.021). When stratified by histotype, a significant increased risk was found for the serous (OR: 1.21; 95% CI: 1.03 – 1.44) subtype while an insignificant increased risk was found for the mucinous (OR: 1.10; 95% CI: 0.80 – 1.52), endometrioid (OR: 1.18; 95% CI: 0.81 – 1.70), and clear cell (OR: 1.08; 95% CI: 068 – 1.72) subtypes. No association with perineal talc use and serous ovarian cancer was found regardless of duration of use (P_{trend} = 0.61). Potential confounders adjusted for included age, education, parity, and oral contraceptive use.

20.0 MOORMAN ET AL. (2009)

In 2009, Moorman et al. used data from the North Carolina Ovarian Cancer Study (conducted between 1999 and 2008) to study the association between perineal talc use and ovarian cancer risk in African American and white women (Moorman et al., 2009). Included in the analysis were 1,086 ovarian cancer cases (143 African American and 943 white women) and 1,057 controls (189 African American and 868 white women). Discussion on talc use was limited and an insignificant increased risk was found for any talc use among both African American (OR: 1.19; 95% CI: 0.68 – 2.09) and white (OR: 1.04: 95% CI: 0.82 – 1.33) women. For the analyses, adjustments were made for age.

21.0 WU ET AL. (2009)

Wu et al.'s 2009 case-control study examined the association between talc use and incidence of ovarian cancer among 609 ovarian cancer cases diagnosed between 1998 and 2002 and 688 controls in California (Wu et al., 2009). A significant increased risk of ovarian cancer was found among women who had ever used talc (RR: 1.48; 95% CI: 1.15 – 1.91) and among women who specifically ever used perineal talc (RR: 1.53: 955 CI: 1.13 – 2.09). Insignificant increased risks were found for talc use on sanitary napkins (RR: 1.61: 95% CI: 0.93 – 2.78), underwear (RR: 1.71; 95% CI: 0.99 – 2.97), and diaphragms (RR: 1.14; 95% CI: 0.46 – 2.87). When assessing frequency and duration of use (reported together), a significant increasing trend was found (P_{trend} = 0.032) and the authors reported the highest risk among long term users (>20 years and >30 times per month; RR: 2.08; 95% CI: 1.34 – 3.23). When looking at total applications, an increasing trend was found (P_{trend} = 0.0004) between no applications and more than 52,000 applications however, the authors noted that for total lifetime applications of talc, "the association was limited to those who started talc use before 1975". Potential confounders adjusted for included race, age, education, tubal ligation, family history of breast or ovarian cancer, menopause status, use of oral contraceptives, and parity.

22.0 ROSENBLATT ET AL. (2011)

In 2011, Rosenblatt et al. studied the association between perineal talc use and incidence of ovarian cancer among 812 epithelial ovarian cancer cases diagnosed between 2002 and 2005 and 1,313 controls in Washington (Rosenblatt et al., 2011). An insignificant increased risk was found for talc use (OR: 1.38; 95% CI: 0.77 – 2.47)

however, it was noted that that few women reported exclusive use of talc and that perineal use of any powder was also found to be associated with an insignificant increase (OR: 1.27; 95% CI: 0.97 – 1.66). No association was found between the use of any powder on sanitary napkins (OR: 0.82: 95% CI: 0.58 – 1.16) or diaphragms (OR: 0.72; 95% CI: 0.48 – 1.10). Potential confounders adjusted for included age, county of residence, number of full-term births, and duration of hormonal contraception use. The authors also reported no trend for duration of use or total lifetime applications of any genital powder.

23.0 KURTA ET AL. (2012)

In their 2012 case-control study, Kurta et al. used data from the Hormones and Ovarian Cancer Prediction (HOPE) study in a contiguous region of Western Pennsylvania and New York and Eastern Ohio (Kurta et al., 2012). Included in their analysis were 902 ovarian cancer cases diagnosed between 2003 and 2008 and 1,802 controls. The authors found a significant increased risk associated with perineal talc use and ovarian cancer (OR: 1.40; 95% CI: 1.16 – 1.69). In their analysis, the authors adjusted for age, race, and education.

24.0 WU ET AL. (2015)

Wu et al. (2015) completed four case-control studies between 1992 and 2008 to evaluate risks of ovarian cancer including talc among non-Hispanic white, Hispanic, and African American women in California (Wu et al., 2015). In total, the authors based their analysis on 1,701 ovarian cancer cases (1,265 non-Hispanic white, 308 Hispanic, and 128 African American women) and 2,391 controls (1,868 non-Hispanic white, 380 Hispanic, and 143 African American women). In the pooled analysis any genital talc use was found to be a significant increased risk for ovarian cancer (OR: 1.46; 95% CI: 1.27 – 1.69). When stratified by race/ethnicity, significant increased risk for any genital talc use was found for non-Hispanic white (OR: 1.41; 95% CI: 1.21 – 1.67) and Hispanic (OR: 1.77; 95% CI: 1.20 – 2.62) women while African American women were found to have an insignificant increased risk (OR: 1.56; 95% CI: 0.80 – 3.04). When examining duration of use, an increased risk was found in the pooled analysis (OR: 1.14; 95% CI: 1.09 – 1.20; per five years of talc use). In their analysis, the authors adjusted for age, menopausal status, age at menarche, hormone therapy use, BMI, income, education, number of live births, oral contraceptive use, tubal ligation, history of endometriosis, and family history of ovarian cancer.

25.0 CRAMER ET AL. (2016)

In 2016, Cramer et al. studied the relationship between talc use and ovarian cancer in 2,041 ovarian cancer cases and 2,100 controls in the United States (Cramer et al., 2016). For their analysis, the authors combined data from three enrollment phases: 1992 – 1997 (Cramer et al., 1999), 1998 – 2002 (Gates et al., 2008), and 2003 – 2008 (Terry et al., 2013). Among women to who had applied talc only to the genital area, a significant increased risk was found (OR: 1.42; 95% CI: 1.04 – 1.96). When reported specifically on the brand of genital powder used, a significant increased risk was found among women who reported using Johnson & Johnson's Baby Powder or Shower to Shower (OR: 1.30; 95% CI: 1.10 – 1.54) and "other brand(s)" (OR: 1.35; 95% CI: 1.12 – 1.64). When examining frequency and duration of use, the authors reported a significant trend in frequency of use (P_{trend} =

<0.0001), "but the trend for years used was flat [P_{trend} = 0.002]". In their analysis, the authors adjusted for reference age and study center and phase. The authors also noted that women who used talc, both cases and controls, were more likely to be older, heavier, asthma sufferers, and regular analgesic users – "none of which was a confounder". When stratified by histotype, there was a significant increased risk for serous invasive (OR: 1.42; 95% CI: 1.19 – 1.69), endometrioid invasive (OR: 1.38; 95% CI: 1.06 – 1.80), and serous borderline (OR: 1.40; 95% CI: 1.03 – 1.90) tumors for women who used any genital talc. A slight insignificant increased risk was found for clear cell invasive (OR: 1.01; 95% CI: 0.65 – 1.57) and mucinous borderline (OR: 1.02; 95% CI: 0.67 – 1.54) tumors while no association was found with invasive mucinous tumors (OR: 0.87; 95% CI: 0.53 – 1.44) for all genital talc users. The authors also analyzed menopausal status and reported that "dose-responses were more apparent for premenopausal women, especially nonsmokers and those heavier or postmenpausal users to menopausal hormones (hormone therapy)".

26.0 SCHILDKRAUT ET AL. (2016)

Schildkraut et al.'s 2016 case-control study of 584 cases of invasive epithelial ovarian cancer and 745 controls enrolled in the African American Cancer Epidemiology Study (AACES; an ongoing case-control study of invasive epithelial ovarian cancer in African American women in Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, South Carolina, Ohio, Tennessee, and Texas) between 2010 and 2015 examined the relationship between powder use and incidence of ovarian cancer (Schildkraut et al., 2016). Study participants were interviewed about any powder use (talc, cornstarch, baby powder, or deodorizing powders) and were considered regular users if they reported use at least once per month for at least six months. The authors reported a significant association between any genital powder use and ovarian cancer (OR: 1.44; 95% CI: 1.11 – 1.86). The authors reported a dose-response relationship when looking at duration of genital powder use (P_{trend} = 0.02) and total lifetime genital applications (P_{trend} = <0.01). The P trend for frequency of genital powder use was found to be <0.01. When stratified by histotype among genital talc users specifically, a significant association was found for both serous (OR: 1.38; 95% CI: 1.03 – 1.85) and nonserous (OR: 1.63; 95% CI: 1.04 – 2.55) cancers. The authors adjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, oral contraceptive use, family history of breast or ovarian cancer, and interview year. Because of recent talc exposure litigation, the authors also conducted analyses on study participants who were interviewed before and after 2014. It was found that there was an increase in reporting talc use after 2014 (before 2014 OR: 1.19; 95% CI: 0.87 – 1.63 and after 2014 OR: 2.91; 95% CI: 1.70 – 4.97) but the authors opined that these results do not support recall bias alone and that "it is possible that the lawsuits sharpened memories of body powder use and improved the accuracy of reported use".

27.0 GABRIEL, 2019

In a case-control study of 4,140 women in Eastern Massachusetts and New Hampshire between 1992-2008, Gabriel et al. sought to determine the potential association between vaginal douching, use of talc powder in the genital area, and risk of epithelial ovarian cancer (EOC). Results from the study indicated moderate association with ovarian cancer among women who used talc but never douched (OR=1.28; 95% CI: 1.09, 1.51) and women

who used talc and store-bought douches (OR=1.53; 95% CI: 1.11, 2.10). Further, no significant association was observed in women who douched but never used talc (OR=0.94; 95% CI: 1.09, 1.51). When compared to women who neither douched nor used talc, moderate risks were observed for serous borderline and serous invasive cancer among women who used talc but did not douche as well as for women who used talc and douched with a store-bought product. One potential limitation of this investigation, as is the case for most case-control studies, is the possibility of recall bias due to study cases disproportionately overestimating prior talc usage. However, the study authors suggested that, based upon a lack of influence of non-genital talc use with ovarian cancer – among other factors – this bias was likely to be minimal. Further, several key risk factors such as familial cancer history (specifically for ovarian cancer), prior asbestos exposure (via household or occupationally), and occupational history were uncharacterized. It is also possible that exposure-related behaviors could have been associated with study participation for either cases or controls, though no data was available to estimate this possible selection influence (Gabriel et al., 2019).

28.0 DAVIS ET AL. (2021)

In 2021, Davis et al. evaluated the association between genital powder use and epithelial ovarian cancer risk among African American (AA) and white women in the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium (Davis et al., 2021). In their review, the authors included the five studies from the consortium that had collected data on body powder use resulting in 3,420 cases (620 AA; 2,800 white) and 7,881 controls (1,146 AA; 6,735 white). The authors examined risk overall, by histotype, and frequency and duration of use. Each study collected exposure data using a standardized questionnaire and genital powder was defined as any type of powder. The authors also excluded women who answered genital powder use questions after 2014 in an attempt to reduce recall bias following talc-related lawsuits that have been filed beginning in 2014. When examining the association between genital powder use and ovarian cancer, the authors adjusted for age, education, duration of oral contraceptive use, family history of breast or ovarian cancer, tubal ligation, full term pregnancies, hysterectomy, BMI, smoking history, and if a participant was pre- or post-menopausal. Among all participants, the authors found an overall increased risk of ovarian cancer (OR: 1.32; 95% CI: 1.17 – 1.48) for ever having used genital powder. When stratified by race, the odds ratio among AA women was 1.22 (95% CI: 0.97 – 1.53) and among white women was 1.36 (1.19 – 1.57) for ever having used genital powder. When reviewing frequency of use (≤ once per week and > once per week) among all participants, no difference in the association was observed (P_{trend} = 0.98). When reviewing duration of use (≤ 20 years and > 20 years) among all participants, no dose-response trend was observed (P_{trend} = 0.97).

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Appendix D

IFRA Fragrance Table

Fragrance Ingredient	CAS No.	Minimum added ingredient (%)	Maximum added ingredient (%)	Maximum combined fragrance ingredients in finished product (%)	Minimum ingredient conc. in total product (%)	Maximum ingredient conc. in total product (%)	Current Category 5 IFRA restriction limit in finished product (%)[#]	Maximum % in finished product is X times less than IFRA standard[†]
FRAGRANCE INGREDIENTS IN JOHNSON'S BABY POWDER								
Benzyl Benzoate	120-51-4	10	25	0.22	0.022	0.055	14	255
Anisaldehyde	123-11-5	5	10	0.22	0.011	0.022	0.84	38
Coumarin	91-64-5	5	10	0.22	0.011	0.022	0.8	36
1-(2,6,6-Trimethylcyclohex-2-en-1-yl)pent-1-en-3-one	7779-30-8; 127-42-4; 1335-46-2	1	5	0.22	0.0022	0.011	16.7	1518
3,7-Dimethyloct-6-en-1-ol	1117-61-9/106-22-9/7540-51-4; 106-22-9; 1117-61-9	1	5	0.22	0.0022	0.011	7	636
Benzyl Alcohol	100-51-6	1	5	0.22	0.0022	0.011	1.4	127
Geraniol	106-24-1	1	5	0.22	0.0022	0.011	2.8	255
5-Isopropenyl-2-methylcyclohex-2-en-1-one	99-49-0; 2244-16-8; 6485-40-1	0.1	1	0.22	0.00022	0.0022	0.6	273
Alpha-Isomethyl Ionone	127-51-5	0.1	1	0.22	0.00022	0.0022	16.7	7591
Amyl Cinnamal	122-40-7	0.1	1	0.22	0.00022	0.0022	5.6	2545
Benzyl Salicylate	118-58-1	0.1	1	0.22	0.00022	0.0022	4.2	1909
Cinnamyl Alcohol	104-54-1	0.1	1	0.22	0.00022	0.0022	0.4	182
Eugenol	97-53-0	0.1	1	0.22	0.00022	0.0022	0.5	227
Hydroxycitronellal	107-75-5	0.1	1	0.22	0.00022	0.0022	1	455
Pentadecalactone	106-02-5	0.1	1	0.22	0.00022	0.0022	1.31	595
2-Acetonaphthone	93-08-3	0.005	0.1	0.22	0.000011	0.00022	0.2*	909
Benzaldehyde	100-52-7	0.005	0.1	0.22	0.000011	0.00022	0.14	636
Cinnamal	104-55-2	0.005	0.1	0.22	0.000011	0.00022	0.05	227
Citral	5392-40-5	0.005	0.1	0.22	0.000011	0.00022	0.3	1364
Cyclamen Aldehyde	103-95-7	0.005	0.1	0.22	0.000011	0.00022	1.4*	6364
Evernia Prunastri (Oakmoss) Extract	90028-68-5	0.005	0.1	0.22	0.000011	0.00022	0.1	455
Methyl 2-(methylamino)benzoate	85-91-6	0.005	0.1	0.22	0.000011	0.00022	0.1*	455
Myroxylon Pereirae (Balsam Peru) Oil	8007-00-9	0.005	0.1	0.22	0.000011	0.00022	0.2	909
Citral	5392-40-5	0	0.005	0.22	0	0.000011	0.3	27273
Opoponax	9000-78-6	0	0.005	0.22	0	0.000011	0.24	21818
Phenyl-acetaldehyde	122-78-1	0	0.005	0.22	0	0.000011	0.1	9091

Fragrance Ingredient	CAS No.	Minimum added ingredient (%)	Maximum added ingredient (%)	Maximum combined fragrance ingredients in finished product (%)	Minimum ingredient conc. in total product (%)	Maximum ingredient conc. in total product (%)	Current Category 5 IFRA restriction limit in finished product (%)[#]	Maximum % in finished product is X times less than IFRA standard[†]
FRAGRANCE INGREDIENTS IN SHOWER TO SHOWER								
Acetic acid, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene	144020-22-4	0.1	1	1	0.001	0.01	1.31*	131
3-Cyclohexene-1-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-	51414-25-6	0.1	1	1	0.001	0.01	0.2	20
Isoeugenol	97-54-1	0.1	1	1	0.001	0.01	0.02	2
FRAGRANCE INGREDIENTS IN BOTH JOHNSON'S BABY POWDER AND SHOWER TO SHOWER								
3,7-Dimethyloct-6-en-1-ol	1117-61-9/106-22-9/7540-51-4; 106-22-9; 1117-61-9	1	5	1	0.01	0.05	7	140
Eugenol	97-53-0	1	5	1	0.01	0.05	0.5	10
Coumarin	91-64-5	1	5	1	0.01	0.05	0.8	16
Amyl Cinnamal	122-40-7	1	5	1	0.01	0.05	5.6	112
Benzyl Salicylate	118-58-1	1	5	1	0.01	0.05	4.2	84
Cinnamyl Alcohol	104-54-1	0.1	1	1	0.001	0.01	0.4	40
Geraniol	106-24-1	0.1	1	1	0.001	0.01	2.8	280
Benzyl Benzoate	120-51-4	0.005	0.1	1	0.00005	0.001	14	14000
Cyclamen Aldehyde	103-95-7	0.005	0.1	1	0.00005	0.001	1.4*	1400
2-Acetonaphthone	93-08-3	0.005	0.1	1	0.00005	0.001	0.2*	200

#Limit values are current through the 48th amendment, as the dates associated with implementation of the 49th and 50th amendment restrictions are in 2022.

**If values were last revised in the 47th amendment or earlier, the percentage listed is for Category 5. If limits were revised in the 48th amendment (denoted by *), values are specifically for category 5D.*

†Rounded to nearest whole number